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Cytoplasmic Inheritance and Intragenomic Conflict

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The differing inheritance patterns of cytoplasmic genes and the sex chromosomes from the Mendelian autosomal patterns can be used to divide the genome into fractions whose defining rule is that the fitness of all genes in a set is maximized in the same way. Each set will be selected to modify the phenotype of the organism in a way which maximally propagates the genes comprising the set, and hence in ways inconsistent with the other sets which comprise the total genome. The coexistence of such multiple sets in the same genome creates intragenomic conflict. Evidence is presented in which the fitness of cytoplasmic and other non-autosomal genetic sets are increased at the expense of the autosomal genetic set. The relationship of such intragenomic conflict to the evolution of anisogamy, dioecy, skewed sex ratios, differential male mortality, systems of sex determination, and altruism is discussed.

1. Introduction

The recent emphasis in evolutionary biology on looking at genes as the unit of selection has focused almost exclusively on nuclear genes. In this context, it is a neglected fact that an important component of hereditary material in organisms is non-nuclear, and perhaps more importantly, that this non-nuclear genetic material¶ is inherited in ways that can be radically at variance with nuclear patterns of inheritance. This creates the potential for conflict between nuclear and cytoplasmic genes, particularly with respect to sex, reproduction, the allocation of parental investment, and altruism towards kin.

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¶ Because no well worked out and consistent terminology exists, for the purposes of this paper we will call genes that exist independently of the chromosomes, and that replicate by an independent process at least part of the time *cytoplasmic genes.* These include plasmids, organelle genes, heritable viral factors, heritable endosymbionts, cytoplasmic genetic factors of undetermined location, preformed structures, and episomes to the extent they reproduce independently of the chromosomes. Synonyms for cytoplasmic genes include extranuclear genes, extrachromosomal genes, plasmagenes, cytoplasmic inheritance, non-Mendelian inheritance, and plasmons.

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Cytoplasmic inheritance is by no means a rare or aberrant phenomenon, but is rather a regular part of the life of every eukaryotic organism (as well as of a large proportion of prokaryotes). Its underappreciation is, perhaps, more a function of the formidable difficulties its investigation presents, than of its unimportance or infrequency. The research program provided by Mendelian genetics draws much of its power from the ability to interrelate data from cytological observation and breeding experiments with theoretical population genetics based on diploid Mendelian segregation. The visibility of chromosomes was an enormous aid in the investigation of nuclear genetics. In contrast, the invisibility or relative unidentifiability of many cytoplasmic factors provided a severe handicap. Further, the simple patterns of Mendelian inheritance created a compelling foundation for the elaborations of population genetics, and the success of the new synthesis tended to divert attention away from hereditary phenomena which could not be readily assimilated into that framework. The slow accumulation of evidence of extrachromosomal heredity has therefore, until recently, been confined to a few concentrated studies on convenient laboratory organisms such as yeast and algae, and reports from reciprocal hybridization experiments of traits which proved to be persistently non-Mendelian. The recent proliferation of sophisticated laboratory techniques has circumvented some of these difficulties, and the slow accumulation of data has changed into a flood. By the mid-sixties there were several hundred well-authenticated cases of cytoplasmic inheritance (Sager, 1965), while now they number in the thousands. The field now has its own journal.

The widespread presumption that cytoplasmic genes code only for trivial traits has also contributed to their neglect. An examination of the data rapidly shows this to be false. There is no evidence that cytoplasmic genes code exclusively for any different category of traits than do nuclear genes (Sager, 1965), and no one has provided solid theoretical grounds for supposing they have a different nature or scope of expression. Organelle genes even have their own sites of protein synthesis, as well as their own tRNA and rRNA. Traits controlled by cytoplasmic genes have been described in organisms as diverse as humans, mice, angiosperms, fungi, protozoans, yeast, algae and bacteria. They definitely code for traits which transcend simple intracellular metabolic functions, controlling such significant characters as allocation of reproductive effort in hermaphrodites (Rhoades, 1933), sex ratios of offspring (Poulson, 1963, 1968), organism size (Faulkner & Arlett, 1964), growth rate (Puhalla & Srb, 1967), colony size (Ephrussi, 1953), rate of senescence (Smith & Rubenstein, 1973), competitive ability (Preer, Preer & Jurand, 1974), drug resistance in bacteria, protozoans, fungi, and mammals (Beale & Knowles, 1978), rates of

recombination among nuclear genes (Thoday & Boam, 1956) as well as many others. It may indeed turn out, after further investigation, that cytoplasmic genes are more restricted in their action than other genes. (There is certainly far less cytoplasmic than nuclear DNA.) But this must be demonstrated, not assumed. And, as will be seen, cytoplasmic genes are quite capable of producing enduring phenotypic effects contrary to the selective interests of nuclear genes.

The recent rapid expansion of empirical findings has not been matched by any comparable examination of its implications for evolutionary theory. Because cytoplasmic inheritance is a phenomenon of presently unknown but potentially large importance, it would seem only prudent to attempt to integrate it with the body of current theory. Accordingly, the heuristic strategy that will be pursued in this paper will be to explore how selection would be expected to act if cytoplasmic inheritance were of some significance, and to compare the results of such analysis against what is found. Because of the potential for the serious underestimation of it as a factor in evolution, the intent is to see how far such analysis can be taken. If the consideration of cytoplasmic inheritance were to make any substantial modification in the way evolutionary processes are presently thought of, it would be in those areas where selection pressures on plasmagenes sizeably differ from those on nuclear genes. Where the interests are in harmony, of course, predictions made on the basis of nuclear genes would hold true for cytoplasmic genes. Because of their different patterns of replication and segregation, plasmagenes will be selected to have characteristics in greatest conflict with nuclear genes involved in the various aspects of sexual reproduction and social behavior. The potential relevance of selection on cytoplasmic genes to understanding the following problems will be discussed:

(i) the cost of meiosis;
(ii) the evolution of anisogamy;
(iii) transitions between hermaphoditicism and dioecy;†
(iv) sex ratio theory and mechanisms of sex determination;
(v) conceptualizing relatedness and the analysis of the evolution of altruism.

2. Intragenomic Conflict

One other factor that has slowed the integration of cytoplasmic genetics with current evolutionary thinking is that those geneticists who are most

† In order to simplify discussion, *hermaphroditicism* and *dioecy* will be used to mean the consolidation of sperm and ova production in the same organism, and the separation of sperm and ova production among two sexes, respectively, regardless of whether plants or animals are under discussion.

closely acquainted with its characteristics are still working within a tradition which found it most productive to see selection as taking place on the organismic level. As a result, nuclear and cytoplasmic genes were seen to be symbiotic participants in a co-adapted genome. Indeed, there can be little doubt that a great proportion of cytoplasmic gene expression does act symbiotically with nuclear genes—for example, in cellular metabolism—because for those functions, selective interests are in harmony. It is precisely there, though, that a consideration of cytoplasmic inheritance has least to say that is fundamentally new about the dynamics of the evolutionary process. It is only in examining those situations where one can expect conflict that different expectations about the outcome of the evolutionary process emerge.

The recent shift towards viewing the gene as the unit of selection, coupled with a recognition of the different modes of genetic inheritance makes the concept of parasitism, symbiosis, conflict, co-operation, and co-evolution—which were developed with reference to whole organisms—relevant to genes within an organism. The idea of conflict between genes within an organism is, of course, scarcely new, though it has been limited to a consideration of conflict among nuclear genes. Blick (1977) analyzed such conflict with respect to Trivers's (1974) concept of parent/offspring conflict. The phenomenon of meiotic drive provides empirical support for the primacy of genic selection over individual selection. There is such conflict among autosomes (Lewontin & Dunn, 1960), and perhaps more interestingly, between either sex chromosome and the rest of the genome, especially with respect to the sex ratio (Hamilton, 1967).

Margulis's (1970) symbiotic theory of the origin of eukaryotic cells is also of interest here, since the hypothesis—though emphasizing the co-operative elements of the relationship between organelles and their "host" cells—provides the phylogenetic basis for an independent assessment of fitness and a potential divergence of interest. She sees the precursor of the modern eukaryotes as a prokaryote which engulfed but could not digest other prokaryotes. These prokaryotes, like many modern strains, retained their capacity to replicate within the host cell. Through coevolution the host DNA became nuclear DNA and the parasitic prokaryotes became the symbiotic mitochondrial and chloroplast organelles. While the system of eukaryotic meiosis and mitosis allowed the nuclear DNA to vastly expand beyond prokaryotic size, the mitochondria and chloroplasts, as is common with obligate parasites, lost their redundant DNA and traits. If this hypothesis is correct, it should be remembered that the transition from an initial relative parity of genome size to subsequent erosions of organelle DNA would be made solely on the basis of the fitness of these endosymbionts, not of the host

cell. Characters increasing their fitness at the expense of the host would show no tendency to be lost in the process of coevolution, even in what is an otherwise symbiotic relationship.

The view that will be developed here is that since there is not a unitary correlation between the potential sets of phenotypic characteristics which maximize fitness for various subsets of the genome, intragenomic conflict will occur. It is therefore useful to divide the genome into fractions whose defining rule is that fitness of all genes in the set is maximized in the same way. Such a set of genes that replicates together will be called a *coreplicon.* Each coreplicon will be selected to modify the phenotype of the organism in a way which maximally propagates the genes comprising that set, and hence in ways inconsistent with the other coreplicons which comprise the total genome. As a result, the fitness gains of one will be the fitness decrements of the others, and therefore the different fractions of the genome will be under continuous active coevolution in a manner analogous to Van Valen's "Red Queen" hypothesis (1973). This suggests that the particular sequence of intragenomic events may explain major trait sets in a way that the simple appeal to ecological circumstances by themselves cannot. This gives an unstable, interactive, and historical character to the evolutionary process, involving both stochastic processes and qualitative differences among the coreplicons in the determination of the particular sequence of adaptations and counter-adaptations that evolve along a given phyletic line.

While other such classifications of the genome into coreplicons (or "communities of interest") are possible and useful, for the purposes of this article it will be divided up as follows:

(i) autosomal genetic material (and obligate Mendelianly segregating plasmagenes where they exist);
(ii) maternally inherited cytoplasmic genes;
(iii) paternally inherited cytoplasmic genes (where they exist);
(iv) male chromosomal sex determining factors, if they segregate independently of the autosomes;
(v) female chromosomal sex determining factors, if they segregate independently of the autosomes.

Competition will go on within each category of hereditary material between different alleles or homologues, while *conflict* may go on between the various categories of hereditary material. Because each fraction of the genome has consequences on the fitness of the other coreplicons through its contribution to the determination of the phenotype of the organism, two coreplicons will be in conflict or in harmony to the extent that the propagation of one correlates negatively or positively with the propagation of the other. The single most important factor in determining the relative

alignment of the interests of the various coreplicons in the genome is the mechanism of sex determination, since it determines which coreplicons reproduce together. Because of this central role, it is expected that the mechanism of sex determination will be a locus of conflict, and hence of active evolution. Such intragenomic conflict is the only extant explanation for transformations in systems of sex determination, as no one has successfully advanced a hypothesis to account for it at the level of individual selection. To date, the exploration of these issues has been confined to the examination of the competition among nuclear alleles, and some analysis of the conflict between sex chromosomes and autosomes (Hamilton, 1967). To this, we would like to add analyses of:

(a) the competition among cytoplasmic genes, and
(b) the conflict between cytoplasmic genes and the various coreplicons of nuclear genes.

First, however, it is necessary to deal with the question of the relative "power" of the different genetic factors. It has been suggested (Alexander, 1974; Leigh, 1977) that no part of the genome can act to any great extent against the interests of the rest, or it will be rendered inert by the rest of the genome through balancing selective processes, constituting a sort of "parliament of the genes" (Leigh, 1977) where all act equally to produce the phenotype. There are a multitude of empirical exceptions to this, from driving sex chromosomes to cytoplasmically induced pollen sterility, and solid theoretical reasons for believing this is not the case. Reasoning from analogy with whole organisms, the zero-sum nature of much competition does not lead to an equality of position either among conspecifics or between species. Extinction or any proportion of balance is possible. Evolved anti-predator traits can be wholly or partially successful, or may be rendered completely ineffective. Within the causal network found in cells, the complexities of biochemical pathways, the sensitivity of morphogenesis, the differential effects of environmental fluctuations, the varying functional interdependence and independence of different loci, the complexities of gene activation and inactivation, the different rates of mutations and back-mutations at different loci, the intricacies of protein synthesis, the differing roles of various hereditary factors at different parts of the life cycle, the distribution and multiplication of various cytoplasmic genes within a given cell, the selection which occurs within an organism between various cytoplasmic genes, and so on, provide a situation dense with asymmetries that give advantage to some genetic factors at the expense of others. It is highly implausible that for every possible mutation there exists an immediate and reciprocal reversible selection possibility which would exactly cancel the exploitive phenotypic effect. For that matter, since the uniparental modes of

inheritance that predominate among cytoplasmic factors, and the biparental inheritance that predominates among sexually reproducing nuclear genes are irretrievably at variance, for many phenotypic traits (e.g. sex ratio) there is no possible state of affairs in which the different genes could be in harmony. What is suggested here is that cellular and morphogenetic processes give wide scope for the asymmetric operation of both nuclear and cytoplasmic factors, with particular phylogenetic and circumstantial factors determining what balance competing forces arrive at in determining a given phenotype. For cytoplasmic–nuclear genetic conflict to be an important phenomenon, it is not necessary for macro-organismic effects to be a widespread property of cytoplasmic genes, only that a few cytoplasmic genes have significant and uncounteracted effects. They could do this in a fashion analogous to that hypothesized for regulatory genes, which may influence the phenotype out of all proportion to their frequency (King & Wilson, 1975). Indeed, cytoplasmic genes may on occasion be regulatory genes for nuclear material. The case of the nuclear mutant *transformer* which changes females of *D. melanogaster* into normal but sterile males shows how easily one gene can overrule the effect of even a large number of functionally integrated genes (Sturtevant, 1945). Similarly, viral infections show how small amounts of DNA or RNA can transform the functioning of much larger amounts of host DNA to serving its selective interests. In any event, it is important to bear in mind that only a small minority of nuclear and cytoplasmic genes in a few species are mapped at all, and the biochemical interactions by which phenotypes are produced are even less well understood. In the absence of a more detailed picture, there seems to be no sure way of deciding in advance what genetic factors will prevail. One expects that there will turn out to be general trends and taxonomic patterns, but at present the best that can be done is to show that in specific cases different categories of genetic material, including the cytoplasmic, have prevailed, biasing phenotypic events in their direction.

3. Cytoplasmic Inheritance

The categories of cytoplasmic hereditary factors include:

(i) mitochondrial and chloroplast genes (these will be referred to as *organelle genes*);

(ii) endosymbionts and parasites which are heritable, including viruses, bacteria, fungi, and algae; some are, in addition, facultatively infective;

(iii) bacterial plasmids; because the topic is restricted to evolution in eukaryotes, this phenomenon will not be further discussed;

(iv) eukaryotic plasmids; eukaryotic cells have recently been found to contain populations of small polydispersed circular DNAs; observations have been made in a variety of species and tissues, including humans, monkeys, and mice (DeLap *et al.*, 1978);

(v) preformed structures; some cell constituents maintain physical continuity in heredity, and their origin is not easily attributed to nuclear DNA (Sonneborn, 1963); Beisson & Sonneborn (1965) demonstrated that the mouth and the contractile vacuole of the cortex of the *Paramecium* can be transmitted from one cell generation to the following independent of the transmission of nuclear DNA or other cytoplasmic factors; the basis for this is the fact that many DNA-produced proteins locate their sites for deposition on the basis of the prior arrangement of already formed cell constituents; thus, parts of the physical organization of the cell are used as templates for assembly, and if they are altered or lost such changes are heritable; such self-perpetuating cell constituents probably include centrioles, which in most taxa cannot arise except from other centrioles;

(vi) cytoplasmic hereditary factors of undetermined location; many non-Mendelian traits have not yet been localized, and while it is likely that all will eventually be ascribed to known categories of inheritance, the possibility of additional categories cannot be ruled out.

Maternal inheritance overwhelmingly typifies cytoplasmic hereditary factors, a fact which is only partially the result of the greater amount of cytoplasm contained in eggs. There are, however, many cases of biparental and paternal inheritance. Centrioles may be exclusively transmitted through the male in most taxa (Jinks, 1964), as the centriole is essential to the flagella which make sperm motile. Such paternal inheritance may explain such phenomena as pseudogamy, where the male of the sibling species contributes the centriole essential to the development of the zygote. Viral factors which are transmitted through the female may sporadically be transmitted through the male (Grun, 1976). Organelle genes in a few species may similarly show a biased yet biparental cytoplasmic inheritance. In the remainder of the paper, unless otherwise specified, when plasmagenes are discussed it is preponderantly or exclusively maternally inherited plasmagenes that are referred to.

The transmission genetics of cytoplasmic genes are profoundly different from the familiar Mendelian patterns of the nuclear genes, and far more complicated. The replication and segregation processes for mitochondrial and chloroplast genes have been the most extensively studied of the plasmagene systems, and will serve to outline many of the major differences between cytoplasmic and nuclear heredity. The following account draws heavily on the comprehensive review by Birky (1978). The "*E. coli*"

of organelle genetics are *Chlamydomonas reinharttii*, an algae, and *Saccharomyces cerevisae*, baker's yeast. The chloroplasts and mitochondria of these species each have their own, unique, extrachromosomal DNA. Unlike nuclear genes, these DNA molecules are circular like those of prokaryotes, and each circle contains a complete set of organelle genes (one circle = one molecule = one genome). The organelle genome codes for rRNA, many tRNAs, and various polypeptides used in cell respiration and photosynthesis. It relies on the host, that is, the nuclear genome, to code for many of the organelle's components. The nucleus contains no copy of the organelle genome and if the organelles are destroyed the nucleus cannot reconstitute them.

Nuclear genes are found only in the nucleus, and there is usually only one nucleus per cell. Organelle genes are usually contained in the mitochondria and/or the chloroplasts, which typically exist in multiple copies per cell. Further, there may be hundreds of copies of homologous organelle genes per organelle, thousands per cell. These organelle genomes are often localized in areas of the organelle called nucleoids, and there may be many nucleoids per organelle. Because there can be many homologous organelle genes per cell, there can be many different alleles as well. Such a cell is said to be heteroplasmic (as contrasted with homoplasmic). The existence of genetically variegated populations of organelle genes in a cell has led to its being characterized as a problem in intracellular population genetics (Birky, 1978). The character of the output frequencies of the organelle genes (i.e. their representation in progeny) is a function of the input frequencies (present in the parents), random drift processes, "mating" (one recombination event between DNA molecules is called a mating), and intracellular selection (Birky, 1978). Many workers (Dujon, Slonimski & Weill, 1974; Goldthwaite, Cryer & Marmur, 1974; Boker *et al.*, 1976; Perlman & Demko, 1974; Birky *et al.*, 1978) have found that (for sexually produced progeny), the output frequency of various organelle genomes reflects their input frequency from the gametes. The bias in input frequency can be due to large discrepancies in the organelle DNA content of maternal and paternal gametes, the extra rounds of "premating synthesis" of mitochondrial DNA (mtDNA) which mating cells undergo in response to mating hormones (Sena, 1976), selection against a particular genotype in the gamete (Kung *et al.*, 1975) and zygote (Chiang, 1976), or bud position in species like yeast (Callen, 1974; Strausberg & Perlman, 1978). As will be discussed later, input biases can be important in maintaining uniparental inheritance patterns.

There are two basic random drift processes. The first, called SMAC for *s*tochastic *m*ating *a*nd *c*onversion by Birky & Skavaril (1976) is simply the

random drift of gene frequencies through recombination and gene conversion, resulting in the fixation or loss of alleles. This process is most important in creating homoplasmia in small subpopulations of molecules, as are found in the nucleoids. The second process is called *random replication* (Birky & Skavaril, 1978). Unlike nuclear genes, organelle genes can replicate many times per cell cycle, and the replication may have a random component. Thus, one or a subset of the genomes may, by stochastic processes, be replicated disproportionately many times (Bogenhagen & Clayton, 1977).

The segregation of nuclear genes is usually restricted to meiotic divisions. Organelle genes, however, regularly segregate during mitotic cell divisions. This vegetative segregation is so general a phenomenon that it is sometimes considered a "law" of organelle genetics (Birky, 1978). Thus, a heteroplasmic cell can produce homoplasmic daughter cells during the vegetative cell cycle. This vegetative segregation is usually attributed to the random segregation of organelles during cell division, but there is growing evidence that it is non-random (Sager, 1972, 1977; Sager & Ramanis, 1976; Singer, Sager & Ramanis 1976).

While logically, organellular inheritance could be maternal, paternal, or biparental, no species with exclusively paternal inheritance has been observed. Moreover, maternal inheritance so overwhelmingly characterizes organelle genes that it, too, has been called a "law" of organelle genetics (Birky, 1978). The cases of biparental inheritance that do exist are characterized by a disproportionately larger maternal contribution.

There are a variety of mechanisms by which maternal inheritance takes place. Anisogamous species show the simplest ones. Organelles may fail to enter the sperm (crayfish, some plants), their organelles may fail to enter the ovum, paternal organelles may be destroyed in the zygote (mammals and algae) or there may be so few that they cannot be detected experimentally (Birky, 1976; Jinks, 1964; Hageman, 1976; Paolillo, 1974). More complicated mechanisms may come into play in organisms that show both maternal and biparental inheritance, such as *Chlamydomonas* and the geranium, *Pelargonium*. Sager (1977) has proposed a model to explain the production of maternal zygotes (MZ), biparental zygotes (BPZ), and paternal zygotes (PZ) in *Chlamydomonas*. *Chlamydomonas* is isogamous and has two mating strains, mt^+ ("maternal") and mt^- ("paternal"). She suggests that the cpDNA (chloroplast DNA) from the two strains are differentially marked, perhaps by methylation of the mt^+ cpDNA, and that linked to the mt^+ allele is a gene that produces a restriction enzyme which degrades the unmarked mt^- cpDNA. If degradation is complete (and it usually is) the zygote has only cpDNA which comes from the "maternal" parent. If degradation is

incomplete or does not occur at all, the zygote is biparental. If the mt^+ cpDNA is inhibited, either experimentally or by the "mat 1" mutation on the mt^- cpDNA, "paternal" zygotes are formed.

Chiang (1976) suggests that the cpDNA from both parents is destroyed in the zygote, but that the paternal cpDNA is destroyed faster. Sears, Boynton & Gillham (1977) also believe that parental DNA is continuously destroyed during zygospore maturation, but that paternal cpDNA is destroyed earlier or faster.

In yeast, the production of MZ, BPZ, and PZ depends on the zygote receiving an input bias from one parent or the other. Birky *et al.* (1978) suggest that the existence of an input bias might trigger a second mechanism which destroys the minority alleles. Whether this process involves a random element akin to "random replication" (Adams *et al.*, 1975; Gillham, Boynton & Lee, 1974) and/or SMAC (Sears *et al.*, 1977 and Van Winkle-Swift, 1977), or is the result of a destruction mechanism arising from competition between the maternal and paternal cpDNA is not known. It could be that the process producing input bias in these species is actively destructive while the later phase which produces uniparental (rather than highly skewed biparental) inheritance is stochastic (Birky, 1978). In any case, the mechanisms producing uniparental inheritance differ widely from species to species, indicating similar selective pressures leading to convergent evolution.

The active destruction of competing cytoplasmic factors suggests that the primary selection pressure involved is competition between cytoplasmic genes for the reproductive resource the zygote represents. The cell is not a single replicating system from the point of view of the cytoplasmic genes, but rather an environment within which selection acts. Nuclear genes replicate only when the cell replicates, and then only once; their rate of replication is limited by the duration of the vegetative cell cycle, and by the rate of organismal reproduction. Cytoplasmic genes, on the other hand, proliferate throughout the cell cycle. Ultimately their reproduction is indeed tied to the success of cellular reproduction, and this leads to kin and group selection pressures on the plasmagenes both within and among cells. Nevertheless, within the cell cycle there is the opportunity for continuous selection between competing plasmagenes, especially at zygote formation. As will be discussed in the section on anisogamy, this competition appears to have had major evolutionary consequences.

4. The Evolution of Sex

Despite G. C. Williams's (1975) and J. Maynard Smith's (1978) pioneering analyses of the evolutionary dynamics of sex, the area still contains major

difficulties. The most intractable of these is Williams's conclusion that the "cost of meiosis" is not offset by the benefits of producing genetically diverse offspring among low fecundity sexually reproducing taxa such as birds, fish, mammals, and reptiles. The recognition of discrete fractions of the genome, each with its separate dynamics and resultant interests, necessitates a re-examination of which parts of the genome suffer the costs of sexual recombination, and which parts benefit by it. In this context it is interesting to note that the cost of meiosis is suffered only by nuclear genes, while uniparentally inherited cytoplasmic genes are not diluted.

Prokaryotic sexual recombination through conjugation presents no anomaly to current evolutionary thinking, and hence the recent questions about the functions of sex apply primarily to diploid eukaryotes. If one finds Margulis's scenario for the emergence of eukaryotes plausible (Margulis, 1970), one immediately notes that for the invading prokaryotic proto-organelles, there is an immediate and severe decrease in the genetic diversity available through conjugation. Instead of a panmictic breeding situation, the proto-organelles would be constrained to mate solely within the host. Especially in the cases of uniparental inheritance, the relatedness between organelles would be extremely high. Even if one finds Margulis's scenario implausible, and accepts the hypothesis that organelles are the result of intracellular differentiation, the lack of recombinant opportunities remains a reality.

The injection of a consideration of cytoplasmic genes into the analysis of sex leads straightforwardly to the following observations.

(i) In organisms where cytoplasmic genes are maternally inherited, only the nuclear genes incur the cost of meiosis.

(ii) Any benefits that result from nuclear recombination accrue to cytoplasmic genes.

(iii) Cytoplasmic factors are frequently involved in structures like spindles which are part of the recombinatory process (Jinks, 1964). Even in prokaryotes, plasmids have the ability to transfer chromosomes during conjugation. In fact, "chromosomal mobilization ability can now be accepted as a common property of plasmids rather than one limited to a few, intensively studied examples" (Holloway, 1979). Direct intervention by plasmagenes in nuclear recombination rates has been reported by Thoday & Boam (1956) and Lawrence (1958).

(iv) In species with maternal inheritance, sperm production or the production of males will be a complete loss to the cytoplasmic coreplicon. The plasmagenes will be selected to encourage reception of ova-fertilizing sperm, but not the production of such sperm. If one

views the cost of meiosis as the cost of producing males (Maynard Smith, 1978), while nuclear genes always incur a one-half cost, cytoplasmic genes may sustain any size cost; the more females produced, the smaller the cost becomes.

It remains to be investigated to what extent plasmagenes are parasitizing the genetic diversity of the nuclear genes, or otherwise adjusting recombination rates. Cox & Gibson (1974) have shown experimentally that a mutator gene may successfully spread in a population by linkage ("hitch-hiking") with resultant favorable mutants it creates elsewhere in the genome. Cytoplasmic genes regulating sexual recombination in nuclear genes in a female biased population would clearly benefit by an analogous hitch-hiking effect, while eluding the attendant cost of meiosis.

5. The Evolution of Anisogamy

Though Parker, Baker & Smith (1972) have developed an interesting set of models to account for the evolution of anisogamy, the mutual consideration of nuclear and cytoplasmic genes provides an alternative model which requires fewer initial assumptions. If the simple view is taken that organisms are resources cytoplasmic genes exploit for their propagation, various data fall into place. An examination of contemporary isogamous organisms reveals processes which strongly suggest what a major selection pressure on gamete size must have been.

As has been discussed, attending upon gamete fusion in many species, a number of signs appear strongly indicating a "struggle" between structures of the two merged cytoplasms over the reproductive resource represented by the zygote. In the zygotes of some mammals paternal organelles are visibly destroyed, while organelles from the sperm of tunicates and some ferns cannot even enter the egg (Birky, 1978). In addition, plasmid incompatibility and its resultant destruction characterizes all homogenic and some heterogenic plasmids (Novick & Hoppensteadt, 1978). It might be expected that such mutual destruction would be even more severe in species lacking the strong input biases characteristic of anisogamous species. In fact, the situation in the isogamous *Chlamydomonas* is remarkable. Chiang (1976) reports that up to 95% of the cpDNA from *both* parents is destroyed in the zygote, but "paternal" (mating type mt^-) cpDNA is destroyed faster.

In isogamous yeasts, many zygotes receiving input biases quickly become uniparental and transmit only the majority alleles (Birky 1978). Minority alleles appear to be selectively destroyed. Selective destruction has been proposed in other systems. Novick & Hoppensteadt (1978) argue that in cases of incompatibility the dynamics of plasmid destruction require that they be able to determine the replication origin of other plasmids, control

copying number, and have a recognition system for partition. Such factors have led Birky *et al.* (1978) to argue that the reason parental cpDNAs destroy each other is that they are each attempting to create an input bias which would set in motion a second mechanism that eliminates minority alleles. The mutual destruction of cytoplasmic genes inflicts costs on the nuclear genes due to the degradation of mitochondria and plastids vital to cell metabolism. Selection on the nuclear genes would be to minimize such conflict by assisting in the creation of homoplasmia through the destruction of minority alleles. This may take place either after syngamy or prior to fusion during sperm formation.

This situation creates a selection pressure for larger and larger input biases, since the majority genes propagate and the minority genes do not. But there is an upper limit to the number of cytoplasmic DNA molecules a gamete of a given size can hold. Thus, there should be selection on plasmagenes for larger and larger gametes to insure a sufficient input bias. Oogamous species show enormous maternal input biases.

Since success depends on gametes being *relatively* larger, as the average gamete size in the population increases, the selection pressure for ever larger gamete sizes would not diminish, but remain self-sustaining. As a result of this endogenous cytoplasmic conflict, this process produces proto-eggs. But the existence of large numbers of gametes in a population which contain enough cytoplasm per gamete to insure a high probability of survival without any supplementation of cytoplasm from the other gamete creates a significant selection pressure on nuclear genes. Since nuclear genes are not destroyed during syngamy, the selection pressures on them with respect to gamete size are significantly different. They are selected to divide the fixed total reproductive resources among gametes so as to maximize number of offspring times survivorship. In a population containing a large number of proto-eggs, a nuclear mutant which produced a much larger number of much smaller gametes (proto-sperm) would have a disproportionately high reproductive success.

Appealing simply to the differing selection pressures acting on cytoplasmic and nuclear genes, the partitioning of reproductive effort into two radically differing types of gametes emerges naturally from the analysis: nuclear based sperm and cytoplasm-rich eggs. The question of whether this partitioning takes place within a single organism (hermaphroditicism) or between organisms (dioecy) is a complicated one that will be dealt with in the next section.

The following points amplify the analysis:

(i) Cytoplasmic genes in the proto-eggs would be selected to differentially accept as fusing gametes those that were significantly smaller than they were.

Additional cytoplasm provided by a fusing gamete might increase the probability of survival or shorten the time to reproduction, but would pose a major risk in introducing competitive cytoplasmic genes. Indeed, there would be a tendency for cytoplasmic genes in all sizes of gametes to jeopardize the survival of the zygote to some extent by resisting fusion with larger gametes and differentially accepting smaller gametes even when it leads to some probability that the total amount of cytoplasm would be insufficient. For the plasmagenes, a lowered chance of survival for the zygote would be favored over a high probability of being swamped and eliminated by plasmagenes from the other gamete. Such selectivity would also delay fusion and hence generation time. This, in turn, would favor *nuclear genes* increasing the amount of cytoplasm in the gamete, in order to expand the number of gametes acceptable to the plasmagenes and thereby increase the likelihood of survival as well as shorten the time until successful fusion.

(ii) The selection pressure described by Parker *et al.* (1972) against sperm mating with other sperm also applies in this model. The greater number of sperm would increase the rate at which they encountered each other, and they would rapidly evolve discrimination systems since fusion with other sperm would mean death or non-propagation from insufficient nutrient resources.

(iii) As the increasing differential in gamete size leads to a vastly lower probability of cytoplasmic factors from sperm surviving in the zygote, selection will tend to decrease the likelihood of cytoplasmic factors even entering the sperm. As has been discussed, comparative evidence from a wide variety of taxa indicates that often they do not. This increases selection against smaller gametes mating with each other, since in the resulting zygotes components vital to the life of the organism would be missing.

(iv) Since any cytoplasmic genes which compete through input bias mechanisms cannot be passed on through sperm, factors controlling sperm production must be nuclear. (This will be more extensively discussed in the next section.) Sperm will tend to be reduced to the minimum structure necessary to get the haploid chromosome set to the egg.

(v) While maternal nuclear genes would be selected to resist syngamy under anisogamous conditions (the cost of meiosis), cytoplasmic genes would be receptive to the genetic variation provided by gametes, providing there is little risk of destruction by accompanying cytoplasmic genes. This condition is met by sperm.

(vi) Populations which possess a destruction system that operates independently of the relative proportions of cytoplasm contributed by the two parents would not evolve toward differential fusion on the basis of size, i.e. they would tend to remain isogamous. Similarly, species whose nuclear

genome suppressed organellular competition would remain isogamous. Single-celled organisms have a low maximum size on the amount of nutrient resources they can put into a gamete. In addition, such a level would not be far above the isogamous optimum gamete size (or the minimum viable gamete size) leaving only a small range for a bimodal differentiation of gamete size. Selection for larger gamete size would tend to entail selection for multicellularity in order to provide the expanded nutrient basis. Conversely, the larger the parental generation, the more freely such selection pressures can manifest themselves. The smaller the organism, the more likely it is to be isogamous.

Evidence that increases the plausibility of this general scenario can be found in the comparative examination of meiosis and cytokinesis in gamete formation and fertilization. Before gamete fusion, for example, mitochondrial DNA undergo multiple rounds of "premating synthesis" in response to mating hormones. In the meiotic process which forms sperm, the initial meiotic doubling produces four haploid sets of nuclear gene complements, each of which is used to form four equal sized sperm. Cytoplasmic genes will not be selected to alter this situation since they will not be passed on through sperm to the offspring in any case. This is not the case for maternal cytoplasmic genes. As was discussed, to be successful in the input bias competition, they are selected to produce as large a gamete as possible. It therefore would not be in the interest of the cytoplasmic genes to partition themselves equally into four equal sized eggs after the initial doubling of the nuclear complement. Rather, they would be selected to all enter one egg having one nuclear complement and all the cytoplasm. The blocking of equal cleavage of the oogonium accomplishes this. In fact, such a pattern is universal in the animal kingdom (Goodenough & Levine, 1974). After the initial doubling, three of the four haploid nuclear complements are excluded into three small polar bodies which degenerate, leaving one huge haploid gamete, the ovum. If cytoplasmic genes were to modify some pre-existing pattern, this is exactly what would be expected. Furthermore, the absence of polar bodies in plants shows that they are not functionally necessary for the formation of eggs. In addition, because cytoplasmic genes would be selected to modify meiosis only in the female, meiosis in males and females are expected to be independent processes. In addition to the fact that polar bodies occur only in females, this view is supported by the fact that mutations affecting the first meiotic division are limited to one sex or the other (Sandler *et al.*, 1968).

This scenario is robust to a different and smaller set of assumptions than that of Parker *et al.* (1972). They posit that gamete size is controlled on the autosomes and reasonably propose that selection will act so as to maximize

gamete number times survivorship. They find that within an envelope of conditions, disruptive selection will act on gametes which will also come to disassortatively mate. However, they must posit that size discrimination at the time of fusion is impossible for large or intermediate sized gametes, but that it is possible for proto-sperm when they encounter one another. They argue that sperm will develop the ability to disassortatively mate and to overcome any evolved resistance on the part of ova because the more numerous sperm will have greater genetic diversity than the ova. This argument is inadequate, since these genetically diverse sperm when fused into zygotes will be ancestral not only to sperm but also to ova, and these ova will be selected for assortative rather than disassortative fusion. Diversity of either genetic morph will show up in the next generation in both morphs. Further, their model concerns the primitive condition where gametes are free floating, and hence where an increase in the number of sperm increases the probability of fertilization. The results of these initial conditions provide no clue as to why anisogamy typifies organisms which have internal fertilization. In internally fertilizing species, it is not the total number of sperm produced, but rather opportunities for mating which increase or decrease the number of ova fertilized. It is unclear why it should take hundreds of millions of sperm, as it does in many species, to fertilize a single egg. Surely, a far smaller number of larger sperm would be just as successful and contribute more resources to the zygote.

The model derived from considerations of cytoplasmic inheritance avoids these difficulties. Even if gametes have the capability of accepting or rejecting fusion with other gametes on the basis of size, the dominant selection pressure towards having a relatively larger gamete still obtains. Further, instead of a difficulty, it is a prediction of this model that ova will avoid fusion with other ova, and that they will differentially accept gametes that contain significantly less cytoplasm than they. Unlike the selection pressures in the Parker, Baker and Smith model, which evaporate as soon as the initial conditions are transcended, this selection pressure will continue even within species with internal fertilization—where, in fact, anisogamy predominates. A species which produces only a few ova to be fertilized at one time may continue to be inundated by large numbers of small sperm which pose little threat of infection by competing cytoplasmic genes—that is, sperm which are significantly smaller than the ovum. This formulation also eliminates the chief puzzle concerning the difference in size between sperm and egg: why one gamete "allows" itself to be parasitized for resources by the other (the cost of meiosis). From the point of view of at least part of the total genome, fusion with sperm is not exploitive. Of course, there is no inherent conflict between the Parker, Baker and Smith model and the

cytoplasmic model. They can be seen as complementary, each process reinforcing the other.

This approach also leads to a somewhat different qualitative characterization of sperm and ova producers than has been traditional. Since Trivers' (1972) paper, it has been common to regard the qualitative characteristics of the sexes as emerging from the initial asymmetry in investment in sperm and ova, an asymmetry of unspecified origin. But approached at a more fundamental level, a better way of capturing the difference lies in the asymmetry in cytoplasmic inheritance. Cytoplasmic inheritance is the driving engine which produces and maintains the quantitative nutrient investment differences. Accompanying this are the differences in genetic endowment, selection dynamics, and cytoplasmic developmental endowment. Males will be preponderantly subject to selection pressures on nuclear genes, while females offer an expanded role for the operation of cytoplasmic genes and cytoplasmic developmental determinants. There is *no* (non-kin) selection on maternally inherited cytoplasmic genes to be functional in males, since males do not pass them on. This disparity in cytoplasmic contributions to the gamete allows significant features of an organism's phenotype to be determined by the constitution of the ovum regardless of the genotype of the entering sperm. This *maternal effect* is true even of traits coded for on the chromosomes. Tissue differentiation, at least initially, is believed to depend upon the distribution of cytoplasmic factors in the egg cytoplasm (Goodenough & Levine, 1974), at least predominantly from the nuclear genome. Such situations point to the possibility that females are capable of biasing features of the offspring in a direction that is selectively advantageous to them. Thus, nutrient asymmetries in gamete production, differences in plasmagene endowment, differences in the operation of selection, and differences in developmental determinants all qualitatively distinguish females and males, and derive from competition between cytoplasmic genes. Thus, the dynamics of cytoplasmic inheritance may give the male–female phenomenon its most enduring characteristics, investing it with selection pressures which keep it what it is.

6. Hermaphroditicism

In the last section, the problem of the distribution of egg and sperm production within and between organisms was left unresolved. If there is run away selection on plasmagenes for the production of large gametes in a population, then those nuclear mutants who are able to devote their entire reproductive effort to the production of small gametes will have the greatest

reproductive success. The population will partition itself into ova producers (females) and sperm producers (males). As soon as this bimodal difference in gamete size exists, nuclear mutants in the ova-producers which simply decrease the size of gametes to intermediate sizes will have lowered fitness, since the high frequency of fertilization by sperm leads to a zygote with insufficient resources. Once this size dimorphism is established, selection locks the "exploited" ova-producing nuclear genes in. Fisher's (1930) sex ratio argument for nuclear genes leads to balancing selection among the nuclear genes for the equal production of the two morphs.

The evolutionary process described is expected to make anisogamy and dioecy the primitive pattern among multicellular organisms. Certain conditions, however, may lead to the evolution of hermaphroditicism. Nuclear mutants in a foundation population heavily skewed toward ova producers *would* be successful if, instead of reverting to intermediate sized gametes, they instead partitioned reproductive effort *between* sperm and ova production. Of course, complete sperm production would be, from the autosomes' point of view, the most adaptive, but if such mutants do not occur, or are for other reasons unsuccessful, hermaphrodites would be the most successful morphs. For example, there is strong selection for hermaphroditicism in flowering plants, and it is primitive to the taxon (Maynard Smith, 1978). In the first place, the duration of the allocation of resources to reproduction can be extended in angiosperm hermaphrodites since pollen production precedes ripening. Among insect-pollinated angiosperms, the same organs can be used to attract insects for both male and female functions. Further, being sessile leads to sib and intergamete competition, reducing the value of additional gametes of a given sex (Maynard Smith, 1978; Charnov, Maynard Smith & Bull, 1976). These strong selection pressures on autosomes for hermaphroditicism sets up an arena in angiosperms for enduring conflict between cytoplasmic and nuclear genes. This intragenomic conflict may be at least partially responsible for the continual reestablishment of dioecy and parthenogenesis.

In (non-selfing) hermaphrodite populations, the following points are clear.

(i) *Cytoplasmic genes benefit by meiotic reduction of eggs and the reception of nuclear genes from sperm.*

(ii) *Cytoplasmic genes will be selected to avoid the allocation of reproductive effort into sperm production, since no cytoplasmic genes (or few) are passed on through the sperm.*

There is a great deal of evidence that such selection is more than just hypothetical. One of the most widely noted phenomena of cytoplasmic inheritance is induced pollen failure in hermaphrodites, in which sperm

production is blocked by plasmagenes. Plasmagenes, of course, are selected to curtail sperm production entirely if this increases egg production at all, and as Darwin (1877) noted, male sterility does indeed increase seed production. One recent review of cytoplasmically induced male sterility (Laser & Lersten, 1972) described 140 species found in 20 families of angiosperms. Indeed, as Beale & Knowles (1978) have commented, "it seems possible that almost any plant could be bred to produce a cytoplasmic male sterile type."

For autosomes in hermaphrodites, the optimum division of reproductive effort between male and female functions is equal (Maynard Smith, 1971). Such male sterility, in addition to almost halving the propagation of the autosomes, creates an imbalance in the ratio of investment in sperm and eggs, and can be expected to set up strong counterselection pressures on the nuclear genes. Any such sperm-sterile organism could, from the point of view of the nuclear genes, increase its fitness greatly by the restoration of sperm production, especially if the population ratios have been skewed by the cytoplasmic mutant towards egg production.

In fact, nuclear fertility restorer genes are widely documented in such species (Duvick, 1965; Smith, 1968; Becket, 1966; Edwardson, 1970). The ability to breed for cytoplasmic sterility indicates that the phenomenon may be nearly universal, at least in the angiosperms, but is usually masked by the successful counteradaptation of fertility restorer genes. In *Zea maize*, the two cytoplasmically induced male sterilities can be suppressed by several chromosomal fertility restorers. This conflict creates strange patterns among corn plants, in which the offspring of a "male-sterile" may produce pollen because its parent was fertilized by pollen containing the restorers. Then, that fraction of its offspring that did not receive the restorer gene (in the ova) again became a male sterile (Duvick 1965). In *Nicotiana, eight* different cytoplasmic male sterility factors have been reported (Smith, 1968).

This picture of coevolutionary intragenomic conflict is made even more plausible by the regularity with which cytoplasmically inherited male sterility occurs in interspecific and intergeneric crosses (Laser & Lersten, 1972). The continual selection for new male sterility mutants and the coevolution of nuclear restorer genes would lead to a situation in which genetically distant nuclear genomes would be more vulnerable to a given plasmagene than those nuclear genes which had coevolved with it. In such hybrids, nuclear genomes are exposed to what are for them evolutionarily novel male sterilities to which they have not yet evolved countermeasures. Such sterilities are masked in the plasmagenes' ancestral line by their concommitant nuclear suppressors. The increased probability of hybrid male sterility may play a large role in speciation (Grun, 1970) as an isolating mechanism.

Thus, intragenomic conflict may also have significant macroevolutionary consequences.

In most known cases, the male sterility is not the result of some general incapacitation of the organism. Rather, the only cells that are seriously defective are in the anthers, the part of the flower containing the pollen sacs (Flavell, 1974). In *Solanum*, for instance, various cytoplasmic male sterilities manifest themselves in the complete absence of anthers, the formation of empty and shriveled microspores, the failure of the anther pores to open, or the blockage of meiosis (Grun, 1976). In *Zea maize*, for the sterility factor called *T*, the anthers are not even exserted, and under conditions of partial fertility restoration, the anthers are deformed (Duvick, 1965). The specificity of the effects strongly supports the interpretation that such traits are adaptations of the plasmagenes.

In animals the picture is more difficult to assemble, but many of the same principles appear to obtain. Reversions from hermaphroditicism to bisexuality do take place, for example among the marine triclads, trematodes, tapeworms, and tunicates (Benazzi, 1947). There is certainly some doubt as to whether there is an equal ratio of investment in sperm and egg production. Apparently throughout gonadal development in synchronous hermaphrodites there is far more ovarian than testicular tissue (Ohno, 1976). Similarly, Leigh (1977) discusses related hermaphroditic species which put very different amounts of reproductive effort into male functions. The operation of intragenomic conflict may also be a factor in delaying the development of testicular tissue in protogynous asynchronous hermaphrodites such that the population is considerably female biased at any given time.

A number of competing selection pressures follow upon cytoplasmically produced male sterility. The cytoplasmic mutant itself will spread through the population in a manner analogous to that described for an autosomally induced parthenogen (Williams, 1975; Maynard Smith, 1978). Any such cytoplasmic mutant will spread to fixation, and nuclear suppressors specific to that allele will subsequently be carried to fixation, masking the effect. The rate of spread will slow (though not be stopped) when the population becomes very skewed in the local area, and the probability of fertilization becomes reduced. The effects on the autosomes, however, are very different. Because a single cytoplasmic mutation is unlikely to increase egg production in a way that fully compensates for the loss of sperm production, the loss of fitness to the autosomes is likely to be substantial. Selection on autosomes, *within the male sterile strain*, is in three contrasting directions. One is towards fertility restoration, as discussed. If that is not accomplished, parthenogenesis would tend to offset much of the loss resulting from male sterility. In

the absence of these possibilities, selection would favor redirecting the reproductive effort wasted in non-functional male structures into increasing the efficiency of female structures. The progressive dismantling of male structures as the result of selection on the autosomes towards reallocation of the reproductive effort increasingly lowers the probability that sperm production will ever be re-established. If sperm production is not restored relatively quickly in such a strain, the atrophying of male parts may soon make it impossible. In fact, cytoplasmic mutants do not need to cause complete sperm sterility to lead to this result. All that is needed is some modification making the individual's sperm production less efficient than its egg production by a factor greater than the existing egg/sperm imbalance in the population. Selection on the autosomes will then rapidly eliminate male structures, so long as the process of atrophication of the male structures increases the inefficiency of sperm production faster than the population egg/sperm imbalance increases. Thus, nuclear genes in male sterile strains are expected to undergo considerable modification adapting them to be fully efficient egg producers. Hence, those autosomes which have been in a female sterile strain will tend to differ from those in the rest of the population.

A hermaphrodite whose sperm production is suppressed is, of course, essentially the same thing as a female. Such cytoplasmically induced male sterility may constitute the first step in the transition of a hermaphrodite population into a dioecious one. If such a gene becomes widespread, the population will consist of two components, hermaphrodites and an expanding number of "females". If events fail to produce nuclear mutations which have the capability of endogenously restoring sperm production, the excess egg production in the population will create a strong selection pressure on the nuclear genes in the rest of the population to exploit the gamete production imbalance. Nuclear mutations which increase sperm production at the expense of egg production among the hermaphrodite segment of the population will have high fitness. In such an unbalanced population, mutations which curtail egg production entirely and correspondingly increase sperm production will spread the fastest. This will widen the difference between the nuclear genes in the proto-males and the proto-females; or rather, since genes are being exchanged between the two morphs, genetic expression of the nuclear genes will become increasingly differentiated. Thus, one has a hermaphrodite population evolving, in response to a cytoplasmic mutation, into a dioecious one.

Presumably, the efficiencies of being hermaphroditic are substantial for most angiosperms, and hence the transition to dioecy inflicts large costs. The incessant intragenomic conflict between induced male sterility and fertility restoration with the constant risk of the irreversible atrophying of the male

structures would itself select for a genetic basis for the male structures which is difficult to lose. Such a resistant or redundant genetic basis could endure the sometimes protracted periods of sterility without atrophying until a fertility restoring mutant appears that suppresses the cytoplasmic effect. Such a resistant form would incur fitness decrements during the periods of male sterility, but would quickly replace the emergent dioecious form when or if a suppressor should appear. Indeed, it is notable that many apomicts retain male structures long after they have any function (Maynard Smith, 1978). It is suggested that this is a by-product of earlier selection against sporadic periods of male sterility.

7. Dioecy

The emergence of dioecious anisogamy, or the transition from hermaphroditicism to dioecy transfers the locus of intragenomic conflict from gamete size and the allocation of reproductive resources between sperm and ova production to *the sex ratio of the offspring females* produce. Males, of course, pass on no cytoplasmic genes, so all reproductive effort a female invests in the production of males is a fitness loss to the cytoplasmic genes. However, this selection on plasmagenes to bias the sex ratio towards females acts only in females. Since males are cytoplasmically sterile, there is no selection (with a few exceptions to be discussed later) on the cytoplasmic genes in them (in outbreeding populations), thus predominantly ending intragenomic conflict in males between the cytoplasmic coreplicon and the others. Therefore, the establishment of males through intragenomic conflict is a selective *cul de sac*, in which entry into dioecy is far more probable than an exit from it. Intragenomic conflict is far less likely to move a dioecious population back towards hermaphroditicism than are ecological forces acting on the nuclear genes.

In a dioecious population, the selection pressures will be as follows:

In females, cytoplasmic genes will be selected to:

(i) resist any reversion to hermaphroditic form;

(ii) produce as many daughters, and as few sons as possible;

(iii) resist inbreeding more than nuclear genes, since the associated inbreeding depression is not compensated by any increase in genetic concentration.

In females, autosomal genes will be selected to:

(a) produce offspring of the rarer, less invested-in sex. If males are rarer in the population, chromosomes will be selected to counteract the various cytoplasmic and sex chromosomal systems manifesting anti-male bias in offspring production. If females are rarer, the autosomes

will be selected to parallel cytoplasmic genes in moderating male production.

(b) produce an equal ratio of investment where the population invests equally in males and females.

In males, cytoplasmic genes

(a) in outbreeding species will have *no selection on them at all to function properly.*

(b) which are facultatively infectious (and rarely if ever passed on through sperm) will be selected to use the host as a vector regardless of their effect on the male host's reproduction.

(c) which can eliminate the male as a competitor with his female sibs (and other female relatives) for resources will be selected for.

(d) in inbreeding species will be selected to skew the sex ratio towards females.

(e) will be selected to avoid inbreeding.

In males, autosomal genes will be selected to:

(a) produce offspring of the rarer, less invested-in sex. If males are rarer in the population, autosomes will be selected to counteract the various cytoplasmic and sex chromosomal systems manifesting anti-male bias in offspring production. If females are rarer, males will be selected to produce females.

(b) produce an equal ratio of investment where the population invests equally in males and females.

(c) counteract the deleterious characteristics of male-antagonistic plasmagenes.

There are a number of ways cytoplasmic genes could bias the sex ratio towards females:

(1) Androgenic sperm could be differentially killed prior to fertilization.

(2) Androgenic sperm could be differentially prevented from fertilizing the egg at the egg membrane. *Penetration by an androgenic sperm is genetic death to the cytoplasmic genes in that egg.* The existence of systems for the detection and elimination of androgenic sperm would select for nuclear genes that would mask differences between male and female sperm. The existence of mechanisms at the egg membrane for the differential exclusion of androgenic sperm would lead to counterselection on male and female nuclear genes to differentially obstruct, inhibit, or slow gynogenic sperm.

(3) In inbreeding species, plasmagenes in males will be selected to block the formation or transmission of androgenic sperm.

(4) When females are heterogametic, cytoplasmic genes acting at meiosis would be selected to influence the frequency of androgenic to gynogenic ova. This would be difficult to distinguish from meiotic drive. Alternatively,

plasmagenes could cause androgenic ova to degenerate before or after fertilization.

(5) Once the egg is fertilized by androgenic sperm, the plasmagenes in the ovum would be selected to cause the zygote to degenerate. This would prevent any further investment by the mother in male offspring of resources that could be invested then or later in female offspring. Such a process of spontaneous abortion could be viewed as kin-selected "suicide".

(6) Alternatively, cytoplasmic genes expressing themselves in the maternal phenotype could detect and eliminate male zygotes, either before or after parturition.

Early on in development, when investment is minimal, the counter-selection forces on the female nuclear genes to suppress this process would be weak, consisting of the lost investment and the minor component resulting from contributing to whatever sex ratio imbalance exists in the population. As the sex ratio grows more skewed, counter-selection would of course increase. Also, as the embryo was increasingly invested in, the selection pressure on the nuclear genes would correspondingly increase. Thus, while cytoplasmic genes would be selected to induce male mortality wherever this increases, however marginally, the production of females, such mortality should decrease as a function of increasing parental investment. When the female is the heterogametic sex, the selection pressures on the Y chromosome and the plasmagenes will be identical.

One might expect that with the differing adaptive demands that are placed on males and females, it would be most adaptive to differentiate the morphs as early as possible to more effectively equip them for their different roles. The detection and elimination of male morphs by plasmagenes, however, places a selection pressure on them to postpone or minimize differentiation until as late in the developmental process as possible, in order to obstruct whatever such elimination mechanisms exist. In fact, in birds and mammals, a very large proportion of the differentiation is very late in the developmental process. In contrast, it should prove fruitful to examine differentiation in taxa in which no post-fertilization parental investment takes place. In such species, post-fertilization cytoplasmically induced male mortality would not increase the production of females, and so one would expect to see less of it. For that reason, differentiation in such species should take place earlier. The only selection on cytoplasmic genes for male mortality, then, would be if there were competition for local resources between the sexes. One expects, then, that *wherever there is post-fertilization parental investment or local resource competition between the sexes, male mortality should be greater than female mortality during the period of investment and competition.*

The data are largely consistent with these predictions. One has only to look to the genetically best studied group, *Drosophila*, to find numerous cytoplasmic sex ratio biasing factors which lead to preponderantly or entirely female progeny. These factors have been observed in populations of *D. prosaltans* in Brazil (Cavalcanti, Falcao & Castro, 1957), *D. paulistorum* from Columbia (Malogolowkin, 1958), *D. willistoni* from Jamaica (Malogolowkin, 1958), *D. nebulosa* from Haiti (Poulson & Sakaguchi, 1961), and *D. equinoxialis* from Brazil, Puerto Rico, and Santo Domingo (Poulson & Sakaguchi, 1961; Poulson & Oishi, 1973). A cytoplasmic sex ratio factor leading to all-female progeny in humans has also been reported (Leinhart & Vermelin, 1946). Many of the *Drosophila* sex ratio factors display the same interactive relationships with nuclear genes that male sterility factors do in angiosperms: the coevolution of nuclear suppressor genes, the so-called "disrupters" (Poulson & Sakaguchi, 1961). Such sex ratio factors (other things being equal) will spread to fixation in a fashion analogous to a parthenogen, carrying any suppressors to fixation after them. Similarly, cytoplasmic mutants which increase female reproduction while injuring or eliminating male reproduction will spread, carrying along any nuclear suppressors. By the same reasoning as was applied to cytoplasmically induced hybrid pollen failure in hermaphrodites, cytoplasmically induced hybrid sterilities in males supply additional confirmation of the widespread nature of this coevolutionary conflict. However, attention has primarily been paid to these processes as species-isolating mechanisms (Dobzhansky & Pavlovsky, 1967; Ehrman, 1963; Grun, 1976, pp. 182–3), though that is a by-product of the selective forces involved. It is also well documented that vertically transmitted diseases frequently express themselves more damagingly or earlier in males than females, (Grun, 1976, p. 273).

Of course for most species the genetic factors contributing to the sex ratio are not known. Of those that are imbalanced, the great majority are female biased (Trivers, 1972; Hamilton, 1948; Lack, 1954). It is also well known, of course, that males in a great variety of species have a higher mortality rate, both *in utero* and during periods of parental investment. The most well-known theory for this is that advanced by Trivers (1972) concerning the prevalence of male–male competition as a consequence of the greater variance in male reproductive success. He theorizes that because of the zero-sum nature of male reproductive success, males will be selected to expend more metabolic effort pursuing behaviors manifesting certain phenotypic traits if by such activity they increase their relative competitive position as against that of other males. He argues that such expenditure necessarily increases their mortality. While these arguments seem straightforward and probably account for much of the observed juvenile and adult

differential mortality, it carries less force the earlier in the life history the argument is applied. It seems implausible to associate higher mortality among androgenic sperm or fertilized eggs with any phenotypic trade-off significantly increasing the likelihood of the surviving adult males inseminating females. Higher mortality rates preceding significant fetal differentiation seem to point to the same conclusion. It seems preferable to look for causes relevant to that stage of life history. This is especially true, considering the widespread occurrence of bimaturism, since it is difficult to compare the pressure on females for early reproduction with the pressure on later maturing males who are in preparation for deferred male–male competition. Also, Trivers (1972) and others frequently infer differential mortality on the basis of an assumed 1:1 conception or birth rate. The dynamics of intragenomic conflict make it unsafe to assume that the ratio of investment in the two sexes is 1:1, and for species with skewed sex ratios, it seems more parsimonious to see them as the product of skewed conception and/or investment, rather than positing the operation of unobserved factors.

As far as intrauterine mortality is concerned, humans are perhaps the best studied species. Initially, it appears that the female zygote is favored during uterine implantation (Kirby *et al.*, 1967). The sex ratio of spontaneous abortions has been found by all workers to be far more skewed towards males than the sex ratio at birth. Estimates of the sex ratio of spontaneously aborted fetuses have ranged from 1·07–3·47, but the best is probably 1·32 (Guerrero, 1948). As expected, the sex ratio of still births is also higher than that of live births (Renkonen, 1963; McKeown & Lowe, 1951).

8. Mechanisms of Sex Determination

The evolutionary differentiation of a population into pure sperm producers and pure ova producers involves the concomitant emergence of a system of sex determination. Inherent in the creation of an obligate system of sex determination is the creation of additional coreplicons with an associated set of fitness correlations with each other and with the pre-existing coreplicons. The presence of these new coreplicons considerably complexifies and intensifies the intragenomic conflict, leading to an intrinsic instability. As has been discussed, selection on the different coreplicons will diverge as to preferred sex of the zygote, and therefore on the nature of the sex determining mechanism itself. The mechanism of sex determination in a taxon controls which coreplicons reproduce together, and therefore the structure of the intragenomic conflict along that phyletic line. The transition from isogamy to anisogamous dioecy or the transition from hermaphroditicism to dioecy as well as subsequent events along each evolutionary

line need to be viewed with reference to the central role played by the sex chromosomes.

Perhaps the most salient point is that before the emergence of dioecy there exists only two coreplicons, nuclear and cytoplasmic, and as a result of the conflict between them there is the tendency for the population to be skewed toward excess egg production. With the emergence of the new coreplicons, on the other hand, there exists (at least for one coreplicon in one sex) powerful selection to skew the population toward male excess. This additional force magnifies the instability one expects to find in populational sex ratios and in mechanisms of sex determination. The spectrum of conflict is widened, and populations may be expected to oscillate between female excess and male excess, rather than simply between egg excess and gamete parity.

If one adopts the perspective of individual adaptation, one would expect that the mechanisms of sex determination would be selected to be reliable (and hence simple), to produce an equal ratio of investment in the two sexes, and once in place to remain unchanged. In fact, however, when one surveys the comparative literature of systems of sex determination, one finds apparently adaptationally meaningless complexity, manifesting unreliability, aberrations, and (from the individual point of view) waste. There are multiple mechanisms in the same population, intersexes, mosaicism, multichromosomal systems, inert and inactivated chromosomes, systems in active transition, continuous high levels of chromosomal aberration, segregation biases, and sex ratio skews. While it is difficult to find plausible individual adaptation arguments for the anomalous biological patterns that are observed, such patterns are just what one would expect to see if intragenomic conflict were a significant evolutionary force. Because antagonistic coreplicons (those with fitness correlations less than one) will have inconsistent selection pressures acting on them, reliability will be lowered. For example, in a skewed population, a nuclear mutant would be selected to transform the sex of the zygote it entered into the rarer sex at the cost of some probability of creating a sterile intersex instead. Similarly, selection may favor a mutant acting at meiosis to increase the probability that it will enter the gamete at some risk of forming aneuploid zygotes with developmental difficulties. Some coreplicons will be entirely unrelated to offspring of a given sex, and so will be selected to sacrifice such offspring or interfere with the biological processes which produce them. Mutants in various coreplicons may shift zygotes onto the developmental pathway leading to the other sex, "struggle" over the genotype entering the gamete or zygote, or alter resource allocation to gametes or zygotes once their genotype is established. Such selection will act on parental, gametic, and zygotic genotypes. At the level of the

individual, one expects to see a proportion of intersexes, chromosomal anomalies, distorted segregations, and other wasteful developmental aberrations. At the population level, one expects to see skewed or oscillating sex ratios, and systems of sex determination that are undergoing active transformation.

Before proceeding, however, it is crucial to clarify an issue that has been left tacit. In considering the run away selection on plasmagenes for larger and larger gametes in an initially isogamous population, it was suggested that the excess of proto-ova created a selection pressure on the nuclear genes in the remaining gamete producers to produce larger numbers of smaller gametes. However, such a nuclear mutant for the production of small gametes will spread only if some of its gametes, having fused with cytoplasmically induced proto-ova, counteract the plasmagenes to produce small gametes. Similarly, in considering the disruptive selection in hermaphrodite populations which contain male-sterile plasmagenes, it was suggested that the excess of eggs in the population selected for increased sperm production. However, a mutant for high rates of sperm production will spread only if it can take advantage of the female produced eggs to produce more sperm producers. In the alternative case, where all offspring of a cytoplasmically induced female continue to be female, the mutant for high rates of sperm production cannot express itself. After the first generation, it cannot take advantage of the excess of eggs, and hence would show no tendency to spread. Thus, cytoplasmically based female-excess populations are special selective filters, selecting for mutants that can transform (at least part of the time) the cytoplasmically induced female's development into a male morph. (It should be recalled that some proportion of the autosomes in these females have been selected to be efficient females. Only the blockage of sperm production need be coded for by the plasmagenes.) In such female-excess populations, male offspring have the highest fitness from the point of view of the nuclear genes in both male and female. Therefore, reversion to isogamy or hermaphroditicism is unlikely, without some particularly strong ecological advantage accruing to hermaphroditicism.

If cytoplasmic inheritance has the evolutionary impact that has been described, then this intragenomic conflict should shape the nature and taxonomic distribution of the mechanisms of sex determination both in its initial emergence and in subsequent transitions. Mechanisms of sex determination have their origin when the sexes emerge, and the most important feature of the conditions hypothesized to prevail at the emergence of dioecy in any phylogenetic line is *an excess of females*. In either the transition from isogamy to dioecy or the transition from hermaphroditicism to dioecy, the female excess populations provide a selective filter for the capability of

turning at least a minimal proportion (depending on the egg/sperm imbalance in the population) of female produced eggs into male morphs.

The male-determining factors which modify the female egg into a male zygote can be either concentrated on a single chromosome (a sex chromosome) or dispersed throughout the autosomes. In the case where the male-determining factors are concentrated onto a single chromosome and are dominant, male (XY) heterogamy is produced. If the male-determining factors are recessive, the female will be the heterogametic sex. In describing such a situation, the recessive male chromosome will be called the X chromosome, and the female chromosome will be called the Y. The mutant X fusing with a Y gamete from the YY females would form XY females, since the X is recessive. These XY females would produce X and Y eggs, presumably in equal numbers, since initially there will have been no selection on the plasmagenes to differentially exclude Xs. Only the fertilization of these X-bearing eggs by an X-bearing gamete would produce males, thus meeting the requirement that males in some measure be produced from cytoplasmically induced female eggs. These males would have high fitness in such a female biased population, and would displace rival fertilizers. The rapid spread of these XX proto-male gamete producers would end the formation of YY females and replace them with XY females. In this way, the system of female heterogamy would be established. The experimental creation of YY individuals which are phenotypically indistinguishable from XY "normal" females (Humphrey 1942, 1945) lends credence to such a view. It is expected that female heterogamy will be rarer, in that the population must be somewhat viscous for it to establish itself. That, and the fact that a dominant male-determining gene would spread far faster in a female biased population, should mean that its independent evolution will be rare.

Female-biased populations will be a recurrent phenomenon, not simply an initial condition. Since nuclear supressors of plasmagenes will only evolve after the spread of a cytoplasmic mutant, the nuclear supressors will tend to be somewhat "behind" in the coevolutionary process. If such biasing is severe enough and prolonged enough, selection on the nuclear genes will be a generalized favoring of male-determining factors among the autosomes. Such a phylogenetic condition will lead to a "genic balance" system of sex determination, in which the autosomes are male-determining and are superceded in the presence of the female-determining X chromosomes. Thus, XX individuals are female, while XO or XY individuals are male. Such an XO system typifies the great majority of roaches, mantids, phasmatids, crickets, grasshoppers, and dragonflies (White, 1973, p. 581), while an XY genic balance system typifies such groups as *Drosophila* (Bridges 1932).

Subsequent events along a phyletic line can alter these initial patterns, particularly as a result of the creation of male-biased populations. These derived populations, if they are enduring enough, may lead to the generalized favoring of female-determining genes, leading to the rare production of the obverse genic balance system.

The ramifications of intragenomic conflict on the sex chromosomes can be far more intricate than can be developed here, depending as it does on the exact sequence of phylogenetic events, mutations, and evolved countermeasures. Nevertheless, the assymetries in the relationships among the different coreplicons do allow some predictions.

(i) The mechanism of sex determination will be a locus of active evolution. There is a large amount of evidence to show that it is (White, 1973), and, as Maynard Smith (1978, p. 164) has pointed out, there is no good explanation for this phenomenon in terms of individual adaptation.

(ii) Because of the female-excess conditions hypothesized to obtain at the origin of dioecy, male heterogamy will be more frequent than female heterogamy. Again, this is supported by the evidence (White, 1973, p. 574).

(iii) In systems where sex chromosomes offset autosomal tendencies (genic balance systems), the autosomes will more frequently be male-determining and sex chromosomes female determining than the reverse.

(iv) This process should be observable in existing populations, some proportion of which should have two or more systems of sex determination or be in transition between them. This has been found, for example, in wood lemmings (Fredga *et al.*, 1976), house flies (Wagoner, McDonald & Childress, 1974), and the cyprinodont *Xiphophorus maculatus* (Kallman, 1965).

It should be emphasized that the male-determining factors which arise with dioecy and which suppress the cytoplasmic female-determiners will show no tendency to cease their effectiveness once a 1 : 1 ratio of investment is reached. From its own point of view, a Y will always be selected to be a driving Y (as will an X). Only autosomal factors will be selected to produce a 1 : 1 sex ratio, *and only then if they have historically been in a population with a* 1 : 1 *sex ratio.* For example, in a population which has a cytoplasmic sex ratio biasing factor which differentially excludes some proportion of the male-determining Y sperm, selection on the Y *and on the autosomes* in males would be for the intraorganismic production of excess amounts of Y sperm either through meiotic drive or some other mechanism. The appearance of a driving Y with an intraorganismic competitive ability that

can circumvent the cytoplasmic factor would expand through the population showing no necessary tendency to stop at a 1:1 sex ratio, but continue toward male excess. Autosomes will contain factors which bias the sex ratio towards what phylogenetically had been the rarer sex. In a skewed population, the mutant that will spread the fastest is not one which has an equal ratio of investment, but rather one which skews the sex ratio of its offspring entirely towards the rarer sex: in other words, the mutant that competes most successfully intraorganismically. Therefore, the existence of cytoplasmic genes which bias the ratio of investment should tend, more than simply to skew sex ratios in a female direction, to destabilize sex ratios, occasionally leading to male biased sex ratios as a consequence. Intragenomic conflict significantly lowers the probability that populations will be found near a 1:1 ratio of investment in the two sexes.

The picture that emerges is one of instability and oscillation. There is an initial transition to dioecy, in which the excess of eggs produced organizes a system of sex determination, unleashing a system of multisided conflict. The new coreplicons may lead to a population imbalance in the opposite direction, subsequently reorganizing the genome into another system of sex determination. Thus, along a phylogenetic line, there is the possibility of a succession of systems of sex determination, initially organized by female excess and perhaps subsequently reorganized by a period of male excess, and so on. Depending on the frequency of such mutants among the various coreplicons, populations may spend a reasonable proportion of their evolutionary history away from an equal ratio of investment. For a certain set of conditions, the oscillations may be non-damping. Assume the existence of a rare mutant which can suppress a (male heterogametic) driving Y to produce all X-bearing sperm. These will initially be very rare in the female excess population in which the driving Y first appears. These mutant suppressors will not begin to increase in the population until after the driving Y begins to appreciably skew the sex ratio. The population will become appreciably imbalanced towards males, lowering the male fitness and thereby driving down the frequency of mutants which can suppress the X-biasing gene. By the same token, the X-biasing mutant will spread past the 1:1 ratio of investment point before selection begins to increase the mutant suppressor of the driving X. And so on. Adaptation to frequent sex ratio oscillations may involve the capability of facultatively shifting the sex ratio of offspring to compensate. At least one species appears to have this capability. Snyder (1976) found that after experimentally skewing the sex ratio of a population of woodchucks (*Marmota monax*) by removing half of the breeding females, the sex ratio among the young of the following year was 40:89.

Hamilton (1967), in discussing the driving Y phenomenon, says:

> It is surprising, however, that the exceptional latent danger to the species presented by this form of drive has received so little comment; I suggest (and to the best of my knowledge this is the first time the suggestion has been made) that it may help to explain why the Y chromosome is so often inert. A population in which a driving Y mutant was spreading could be saved by another mutation on an autosome or on the X chromosome which was capable of inactivating the relevant region of the Y mutant.

To express this somewhat differently, by tautology, systems which oscillate randomly through a number of different states will spend more of their time in states which are more difficult to exit from. The inactivation, reduction, or complete elimination (as in XO systems) of the heterogametic chromosome reduces or eliminates the probability that a countermutation can evolve. Therefore, species will spend more time in systems of sex determination which have a reduced or eliminated Y. In taxa with male heterogamy, the cytoplasmic coreplicon especially will be selected to reduce or inactivate the Y.

The "elimination" of the Y need only imply that it lose its role as a sex-determiner, with autosomes or a genic balance system replacing the former sex chromosomes in that role. The fusion (or translocation of relevant portions) of the Y with an autosome or an X may have the same effect. This is particularly true if such a process did not block the drive effect. The driving mutant, translocated onto the other sex chromosome, would have especially high fitness in a population skewed in the other direction. Lyon (1974), on other grounds, has suggested that the heteromorphism in mammals between the X and Y is the result of such a transfer of genetic material to the X from the Y. Since they would have been more nearly homologous at the time, such a process would have effectively duplicated much of the X chromosome, necessitating an X-inactivation mechanism in females. There are in fact some indications of internal duplication within the X, but the evidence is inconclusive (Ohno, 1976).

The existence of a sex ratio imbalance creates a selection pressure on the autosomes to increase the probability they are in the rarer sex by increasing their association with the genes determining the rarer sex, for example, by fusion. Similarly, the existence of driving X chromosomes would create a selection pressure on the autosomes for fusions. These factors may help account for the widespread occurrence of such fusions (White, 1957). Fusion with the X in an XO system frequently leads to the emergence of a neo-XY system, with the new Y the fused autosome's homologue. The rapid rate at which these new Ys can become heterochromatinized in evolutionary terms indicates how strong such intragenomic conflict is. Selection for association

with the sex chromosomes determining the rarer sex or with driving sex chromosomes may also contribute to the formation of multiple chromosome systems of sex determination.

In addition to altering probabilities of association with genes determining the rarer sex, selection will also favor genes which transform the sex of the zygotes they enter into the rarer sex. Of course, this pressure on the autosomes is hypothesized to be the origin of genic balance systems. On the sex chromosome associated with the excess sex, selection will act to transform what it coded for. For example, in a male heterogametic population with a driving Y, selection would act on the Y (as well as the X, the autosomes, and the plasmagenes) to transform an XY individual into a female. Initially, this would lead to a population with both male and female heterogamy, as, for example, the wood lemmings, *Myopus schisticolor* (Fredga *et al.*, 1976). Such a process may fixate at female heterogamy, maintain a balanced polymorphism, or result in a different pair of chromosomes taking over the role of sex determination.

The cytoplasmic coreplicon is unique in that for it alone, the sex ratio is irrelevant to the direction of selection. For the plasmagenes, unlike the nuclear coreplicons, it is the *morph* that matters rather than the genotype *per se*. Selection on the plasmagenes is uniformly to over-rule the male determiners, and since in most populations with both male and female heterogamy the genetic basis is not known, cytoplasmic genes may underlie some fraction of these occurrences as well. The case of the gypsy moth, *Pothetria dispar*, studied by Goldschmidt (1931, 1934) illustrates such conflict between cytoplasmic factors and male determiners. *Porthetria* is distributed in a number of geographic races from northern Europe to Japan. In purebred races the cytoplasmically inherited female determiners and the nuclear male determiners appear to be in equilibrium, so that no intersexes are produced. However, the strength of the sex determiners varies from race to race, so that interracial crosses may be arranged to produce a graded series of intermediate intersexes. For example, in mating males from a race with extremely strong male determiners with females from a race with especially weak female-determiners, both XY and XX offspring were completely male morphs. White (1973, p. 579), in discussing *Porthetria*, asks "why, after all, should the strength of sex-determining genes be in a state of active evolution in a particular species?" Such phenomena can be more easily assimilated into the framework of intragenomic conflict.

One other peculiarity of the heterogametic sex chromosome should be mentioned. That is, because of the system of sex determination, it can never be homologously paired with itself, or exist other than heterozygously in an individual. Selection will therefore act on it to strongly avoid any inbreeding,

since it suffers inbreeding depression without any compensating increase in relatedness in the inbred offspring. Therefore, in mammals, males should disperse further while in birds, females should disperse further, as seems, in fact, to be the case.

Trivers (1972) approached dioecy by considering that one could "treat the sexes as if they were different species, the opposite sex being a resource relevant to producing maximum surviving offspring." This formulation, while valuable, requires reanalysis in order to clarify how to quantify fitness from the point of view of the various coreplicons in the genome when the offspring consist of two sexes that are genetically different. From the cytoplasmic viewpoint (in females), since males are cytoplasmically functionally sterile, fitness consists solely in daughters produced. From the point of view of the sex chromosomes, in the homogametic sex offspring of a given sex will be worth the reciprocal of its ratio in the population. For the heterogametic sex, fitness from the viewpoint of the Y chromosome will consist solely of heterogametic offspring, while for the X-chromosome it will consist solely of homogametic offspring. This phenomenon in sex chromosomes has received some attention (see especially Hamilton, 1967), generally confined to the mechanism of meiotic drive. For the autosomes, offspring of a given sex will be worth the reciprocal of their ratio in the population. Fitness being so different for the different components of the genome, conflict of a major nature can be expected.

The fitness of the cytoplasmic coreplicon is:

(a) 100% correlated with the Y chromosome in female heterogametic species.
(b) 100% correlated with the X chromosome in incoming sperm in male heterogametic species.
(c) 100% negatively correlated with the Y chromosome in male heterogametic species.
(d) 100% negatively correlated with the X chromosome in female heterogametic species.
(e) correlated either negatively or positively with the fitness of the autosomes depending on the sex ratio in the population.

Similarly, the fitness of the autosomes positively or negatively correlates with that of the sex chromosomes as a function of the sex ratio in the population. Each autosome is a coreplicon with a 100% negative fitness correlation with its homologue. And, of course, the fitness of the sex chromosomes (in the heterogametic sex) is 100% negatively correlated with each other.

Interactions among the various coreplicons may produce genetic patterns which are very difficult to interpret. Even a plasmagene-nuclear suppressor

interaction may appear to be simply Mendelian, if alternative nuclear alleles are more common than alternative cytoplasmic alleles. The phenotypic differences between individuals would be predicted by a simple Mendelian model, despite the involvement of the cytoplasmic factor. The existence of three (or more) sided interactions would be expected to evolve, with correspondingly intricate patterns of inheritance. For example, in female heterogametic populations, a mutant on the Y which blocked a gene on the X which suppressed a cytoplasmic sex ratio factor would have high fitness. A consideration of the positive and negative correlations between fitnesses among the various coreplicons yields a matrix of modifications and regulatory activity that is to be expected among the genes in the various coreplicons. "Co-operation" or mutual facilitation is expected where the fitness correlation is high, and suppression and disruption is expected where the fitness correlation is low. For example, many cytoplasmic factors exist which are antagonistic to the paternal chromosomes, and which favor the differential propagation of the maternal chromosomes (Grun, 1976, pp. 288–292). In *Epilobium hirsutum*, a program of substitution backcrossing could never be completed because of the cytoplasmic based selective retention of maternal genes (Michaelis & Michaelis, 1948). In *Drosophila robusta*, a cytoplasmic factor selectively broke paternal chromosomes, resulting in a higher rate of transmission of maternal chromosomes (Levitan & Williamson 1965).

Because cytoplasmic genes, autosomes, and sex chromosomes all may segregate and be inherited in differing patterns, there is no resolution to this conflict. The progressive exploration of stable equilibria, from Fisher's (1930) sex ratio argument to Hamilton's (1967) unbeatable strategy to Maynard Smith & Price's (1973) evolutionarily stable strategies (ESSs) rely on the traits occurring at the same locus or at least segregating in parallel Mendelian fashion. These tacit conditions do not apply to the different coreplicons of the genome. The differing coreplicons are not in direct competition with each other, but rather, have consequences on each other in determining what that phenotype will be. It follows than that there is no necessary resultant relationship among them, no evolutionarily stable matrix, no equilibrium. At any point in time, the evolving situation may favor any coreplicon, or lie in any intermediate state. This will depend on the particular biochemical, cytological, morphogenetic and ecological events that have occurred along a given phylogenetic line. Nevertheless, some configurations, such as dioecy, or reduced or eliminated Y's may prove more enduring than others.

The lack of a stable equilibrium in the sex ratio is a result which needs broader recognition. Fisher's (1930) clear and elegant formulation on the

sex ratio with the simplicity of its predictions has proven so compelling that it is often assumed that the ratio of investment in a population is equal. This is particularly true in that the qualitative differences between male and female structures on hermaphrodites and between male and female morphs often make it very difficult to evaluate what the true situation is in a given population. This has led to the widespread impression that the comparative data are overwhelmingly supportive whereas in fact they are ambiguous.

There are numerous reports of mammals with male-biased sex ratios at birth (Asdel, 1964; Schaller, 1972; Hope, 1972; Mech, 1975; Smith, 1968) at least some of which endure into maturity and are not the result of differential mortality after birth (Clark, 1978). Reports of female-biased sex ratios have already been discussed. Cases of male-biasing and female-biasing meiotic drive as well as their associated suppressors are well known (see Hickey & Craig, 1966; Hamilton, 1967) though of course cytoplasmic sex ratio factors can be easily misidentified as cases of female-biasing meiotic drive. Extreme sex ratio swings towards the female have been reported in butterflies (Owen, 1966) though the genetic basis has not been isolated. Such intragenomic conflict should also lead to heritable or contrastingly biased (or unisexual) offspring sex ratios. Numerous cases have been reported, such as Weir's (1962) investigations on mice, and in *Armadillidium*, *Trichoniscus*, *Asellus*, *Cylisticus*, *Porcellio*, and *Tracheoniscus* (White, 1973, p. 606).

It is unlikely that intragenomic adaptations and counter-adaptations will all act in precisely the same stage of the life cycle. If this is true, then another line of evidence that could be developed is the change in sex ratio through the process from spermato- and oogenesis to adulthood. Specific associations of one period of the life cycle with a given coreplicon remain speculative, and dependent on the recent events in the phylogenetic line, but the general prediction is quite clear: sex ratios should shift *in both directions* during the life cycle. For example, in humans it appears that fewer Y-bearing sperm are produced than X-bearing sperm, with estimates of androgenic sperm varying from 34%–43% (Diasio & Glass, 1971; Rohde, Postman & Dorner, 1973; Beck *et al.*, 1976). Subsequently, after penetration of the cervical mucus the percentage of androgenic sperm rises to between 52–58% (Kaiser, Citoler & Broer, 1974; Broer, *et al.*, 1976). Fertilization rates are not known, but as discussed elsewhere, afterwards male zygotes have a higher rate of spontaneous abortion. And of course, immediately after birth, in a large proportion of cultures there is differential female mortality due to differential parental care (Divale & Harris, 1976). To our knowledge, there is no other hypothesis which predicts reversals in the direction of sex ratio change over the life cycle.

The biological processes found in many species give rich opportunity for the asymmetric action (and subsequent intraorganismic countermeasure) of the various coreplicons. Evidence for differential phenotypic control by individual sex chromosomes lends credence to the possibility of bias in reproductive behavior favoring one sex chromosome at the expense of the other. It has been shown that in many female mammals (though not all; Grüneberg, 1969) one of the two Xs is inactivated (Lyon, 1961), though in different tissues of the same female different Xs may be heterochromatinized. Even so, in individuals with such "mosaicism" of heteropycnosis, the division may be by no means equal (Hamerton *et al.*, 1969). In certain species, one X is not simply inactivated but excluded entirely from somatic cells (Hayman, 1969). While dosage compensation may offer a partial explanation, it is difficult to apply such an explanation to such phenomena as the comparable inactivation of the Y (Perondini & Perondini, 1966; Hayman, Martin & Waller, 1969). Significantly, it has been shown that in many species it is uniformly the paternal X which is inactivated (Sharman, 1971). Such inactivation mechanisms give wide scope for the operation of effective intraorganismic competition.

The abberant cytogenetics of the fungus gnats, *Sciaridae*, exemplify the patterns of apparent conflict. In a typical species, *S. coprophila*, chromosomes (the so-called limited chromosomes) are found in the germ lines which do not replicate into the somatic cells (White, 1973, pp. 516–523). In the sperm produced, with the exception of these limited chromosomes, *all the autosomes and sex chromosomes are of maternal origin*, paternal genes having been excluded. In females one paternal X is eliminated from the germ line while in males both paternal Xs are eliminated. Sex determination is controlled solely by an unknown maternal genetic factor acting through the egg cytoplasm. It is also extremely interesting that in many species in this genus females produce offspring of only one sex throughout their lives. Here is unquestionably a case in which certain coreplicons are advantaged in intraorganismic competition. Clearly, gene action not only at meiosis but throughout development can influence the relative reproduction and success of various coreplicons.

A number of proposals involving selection on the autosomes have been advanced to account for the various sets of comparative data that indicate deviations from a 1:1 sex ratio. These have included inbreeding and concomitant local mate competition (Hamilton, 1967), maternal condition when males have greater variance in reproductive success than females (Trivers & Willard, 1973), parent–offspring conflict among eusocial hymenoptera (Trivers & Hare, 1976), differential costs of male and female (Fisher, 1930), and local resource competition (Clark, 1978). The effects of

these selection pressures will be modified to the extent that intragenomic conflict is causing sex ratio oscillations away from the autosomal optimum.

The recent trend has been to view mating systems solely as the product of ecological forces. To the extent that intragenomic conflict produces skewed sex ratios and sex ratio oscillations, it will be a major factor in conditioning the mating system and concomitant adaptations of a species. Correlations between mating systems and sex ratios may derive either from cytological or ecological forces. Intragenomic conflict may be an endogenous engine of evolutionary change which must be paired with the exogenous engine of ecology to completely explain the patterns that are seen. At the very least, some residual puzzles (such as the polyandrous birds) may be resolved.

9. Coreplicons and Relatedness

While Darwin (1859), Haldane (1955), and others recognized that traits may evolve because of their effects on relatives, it was not until the publication of Hamilton's (1964) pathbreaking paper that that insight was explicitly developed into a coherent model of the evolution of social behavior. Initially, Wright's coefficient of relationship was used to specify conditions under which altruism and selfishness can be expected to occur, though more recently other coefficients have been defined for this purpose (see, for example, Orlove & Wood, 1978). With the exception of haplodiploidy, such formulations tend to deal only with nuclear genes inherited in Mendelian patterns. The recognition of discrete fractions of the genome, each with differing probabilities of presence and reproduction in other individuals considerably complexifies such analysis.

Regardless of the coefficient used to measure relatedness, values between two individuals will differ depending on which coreplicon is being referred to. As a result, there will be intragenomic conflict over how altruistic to be to a given individual. To conceptually capture these differences, the use of Wright's coefficient of relationship (r) will be clearest, though others could be employed. For the heterogametic sex chromosome, relatedness will be effectively clonal for all heterogametic members of a given lineage. Thus, where females are heterogametic, for this coreplicon all females descended through female links from a common female ancestor are clonally related to each other, and unrelated to any other individual. Similarly, where males are the heterogametic sex, all patrilineal patrilaterally related males are clonally related in their heterogametic sex chromosome coreplicon. Hartung (1976) has discussed the potential implications of this for humans. For the homogametic sex chromosome, relatedness can be found by path analysis, where in the heterogametic sex links to homogametic offspring have a

1·0 probability of passing on the chromosome and links to the heterogametic offspring have a 0 chance of passing on the chromosome. All other links are 1/2.

For a given cytoplasmic coreplicon, where p is the probability that a given plasmagene was passed through the female parent, and q is the probability that it was passed through the male parent, coefficients of relationship can be found through path analysis:

$$r_{ij} = \sum p^f q^m \tag{1}$$

summed for all paths, where f equals the number of links through females and m equals the number of links through males. In the event that multiple cytoplasmic coreplicons exist, for example for paternally inherited centrioles and maternally biased mitochondria, relatedness must be calculated independently based on the varying probabilities of maternal and paternal transmission.

However, r_{ij} by itself is not sufficient to describe the selection pressure for altruism on a given coreplicon. To arrive at the coefficient governing trade-offs of costs and benefits between actors and recipients for a given coreplicon, the probability that a given gene, if it is in the organism, will be passed on must be factored in to both actor and recipient. For Mendelianly inherited genes the ratio of these two probabilities is always 1. However, for cytoplasmic inheritance this is not true, and the probabilities are the above defined p for females and q for males. If the actor is female and the recipient is male, $r_{ij}(q/p)$ times the benefit to the recipient must be greater than the cost to the actor. Alternatively, if the actor is male and the recipient is female, the effective coefficient will be $r_{ij}(p/q)$. When the pair are both of the same sex, the probabilities cancel and the effective coefficient is simply r_{ij}. In the mathematically undefined case where $p = 0$, males will not be altruistic toward each other and the effective coefficient is defined to be zero.

In the common case where there is virtually no probability of passing on cytoplasmic genes through the male, females in a matriline will be clonally related. The cytoplasmic coreplicon in such females and males will never be selected to manifest altruism toward male relatives, while selection on plasmagenes in males will be to be completely altruistic towards female kin. To the extent cytoplasmic genes shape social behavior, kin groups are expected to be female based, with females helping their matrilineal matrilateral kin, and males differentially assisting such kin. While surely there are other explanations, it bears pointing out that almost all mammalian social organization is congruent with these predictions. Where the presence of males is more costly than any active assistance they might render (surely the case in the great majority of mammals), males are expected to disperse

and/or suffer higher mortality. In birds, where males can as effectively render assistance as females, differential male assistance would be predicted, and male helpers at the nest are more common than female (Brown, 1975).

For those whose credulity it taxes to posit plasmagenes with an altruistic phenotypic effect, one need only point out that plasmagenes play a known role in disease, and an altruistic act for males who inflict resource competition costs on female kin would simply be to have lowered disease resistance. For example, Leber's optic neuritis in humans is cytoplasmically inherited and expresses itself far more markedly in males than in females (Grun, 1976, pp. 271–276). The greater male susceptibility to disease thus becomes analyzable as cytoplasmic altruism. The correlation of disease susceptibility with male/female natal resource competition may eventually provide a more exacting test of these predictions, as may a closer investigation of the few species with very large sperm.

Unlike the case of nuclear genes, which are usually exactly conserved through the life cycle of an organism, the relatedness of plasmagenes between cells within an organism and between parent and offspring can be significantly modified by mutation, selection, and drift. Heteroplasmia (the existence of two or more cytoplasmic alleles) in an organism can be created by mutation or by sporadic or consistent biparental inheritance. At least some mutation rates appear to be far higher among cytoplasmic genes than among nuclear genes (Sager, 1972, p. 119; Jinks, 1964, p. 68). The creation of heteroplasmia through the survival of paternal plasmagenes is taxonomically extremely variable, in most cases being nonexistent or at undetectably low levels. In those organisms in which there is some paternal contribution to the cytoplasmic inheritance, the reported percentages of progeny which show biparental inheritance range from the very low such as three per thousand up to such high values as the 30% found in *Pelargonium zonale* (Jinks, 1964, p. 39). Occasionally in that species, a few progeny may be found with plastids solely from the pollen parent. Once heteroplasmia is established in a zygote, both drift and selection may take place over mitotic cell cycles to produce low relatedness among different parts of the same organism, and among its offspring. If, for example, there are two cytoplasmic alleles in the zygote, subsequent cell divisions may produce cell lines homoplasmic for each as well as cell lines which remain heteroplasmic. Gametes from an area of the organism that has become homoplasmic of course carry only that plasmagene. For example, in *Mirabilis jalopa*, regardless of the pollen parent, flowers on the green regions of the plant yield only green progeny, flowers on the white regions yield only white progeny, and flowers on the variegated regions yield a wide variety of mixed progeny

(Jinks, 1964, p. 31). Such intraorganismic allelic differentiation can be expected to give rise to intraorganismic conflict, in which various parts of an organism are selected to divert additional resources to their own reproduction.

Selection within and across cell cycles also occurs modifying relatedness. Dauermodifications are the clearest example of this, having been obtained in a wide variety of groups, from protista to insects and higher plants. They are changes in the cytoplasmic gene complement induced by exposing the developing organism to some harsh environmental stimulus such as starvation, extreme temperature, sublethal doses of toxins, and so on. The induced change persists over multiple generations, showing matriclinal inheritance, but slowly reverting back to the ancestral form (if the inducing stimulus has been removed). The reintroduction into normal environments reverses the intraorganismic selection pressures on the organelles and other plasmagenes so that with each generation the within organism percentages gravitate back toward those typical of the ancestral form (Grun, 1976, p. 284). Intraorganismic selection and its consequences on linked genes, potentially high rates of mutation, and drift may all introduce substantial deviations from the expected patterns of relatedness, but more empirical work will have to be done before reliable estimates of the nature of these deviations can be developed.

10. Conclusion

Cytoplasmic inheritance is a phenomenon whose importance in evolutionary processes may have been seriously underestimated, and its dynamics need to be integrated with the body of evolutionary theory. Those who would discount it must deal with the documented fact that in a large number of organisms it has produced major traits which favor it and disadvantage the autosomal coreplicon. This is true of the other, usually neglected, coreplicons as well. While clearly the amounts of DNA in each coreplicon differ greatly, qualitative differences in the location, action, and timing of activation of the cytoplasmic genes may offset simple considerations of quantity. Early in development, the zygotic nucleus plays little role in regulating activity. Further, sequential nuclear transfers and restorations to the original cytoplasm in zygotes demonstrate that even a brief exposure to cytoplasmic factors can permanently alter the operation and expression of the nuclear genes (Moore, 1960). Also, as in the case of the reduced Y chromosome, the quantity of DNA present in a coreplicon may itself be the result of intragenomic conflict.

The resolution of such issues awaits future research, including especially a clarification of the taxonomic picture. The evolution of various groups must have been significantly shaped by the consequences of the presence or absence of such structures as plastids, centrioles, kinetoplasts, and sex chromosomes. There are important indications of major structural differences in relationship among the coreplicons in various groups as well. In fungi, the role of cytoplasm is one of free intercellular transport. In the filamentous ascomycetes, for example, the hyphae have no true cell walls; they are separated into pseudo-compartments by constrictions at the annular thickenings through which the cytoplasm and plasmagenes freely flow. The nuclei of the fungi are small enough to pass through the central pores, but do not do so (Jinks, 1964, p. 68). Such differences in mobility between nuclear and cytoplasmic coreplicons of necessity would structure their relationship in ways that contrast greatly with the relationships found in other groups.

There has been a growing consensus in the literature of viewing the individual organism as a coadapted genome, pursuing unitary goals in response to selection pressures acting in unison on all parts of the genome. This view is unwarranted by the genetic systems which underlie all non-parthenogenic species, and what needs to replace it is the concept of the individual as being comprised of a number of genetic subsets (coreplicons) with enough positive fitness correlations among them that individual reproduction does successfully take place. This transformation of perspective would be comparable to the shift that has taken place over the last two decades from viewing the eusocial hymenopterans as coadapted superorganisms to viewing them as systems within which both co-operative coadaptation and conflict take place. Just as patterns of eusociality are no longer considered simply the product of ecological factors, so major dimensions of individual trait-sets may be the consequence of intragenomic conflict. Endogenous selection pressures cannot be separated from the exogenous, since the most fundamental aspects of reproduction, such as recombination rates, gamete dimorphism, allocation of reproductive effort, sex ratios, altruism, and sex determination have profoundly different selective consequences on the different coreplicons. The fact that selection is in quite independent directions on a number of key features of the phenotype may explain why systems which should, from an individual selection perspective, be simple and reliable are so frequently the locus of active evolution and so filled with "non-optimal" aberrations. Since fitness for all the coreplicons in a genome cannot be simultaneously maximized, this leads to a different characterization of the evolutionary process as well. Instead of a process of convergence on increasingly adaptive forms, or at least a

sequential tracking of ecological shifts, evolution may include the process of selection causing unending oscillations between forms in which one coreplicon is favored to forms in which others are favored.

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