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THE QUARTERLY REVIEW of BIOLOGY



EVOLUTIONARY CONSEQUENCES OF INTRACELLULAR ORGANELLE COMPETITION

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ABSTRACT

The review discusses some consequences of the widespread partial uncoupling of the reproduction of organelle DNA from that of nuclear DNA. I propose that in certain circumstances natural selection favors intraorganismal reproductive competition between different varieties of organelle DNA, and in other circumstances selection favors competition between organelle and nuclear DNA. Evidence is marshalled to show that such competition occurs in nature. Situations which would lead to selection for both kinds of competition are described and are shown to be relatively common. A number of examples of apparent competition of predicted kinds are presented. Several testable predictions are made from the theory, and it is shown that the available data are in accord with them.

Similar kinds of reproductive competition are predicted to occur in some other symbiotic relationships, and possible examples are presented for two of them: bacterial plasmids and endozoic algae.

"There is something intrinsically good-natured about all symbiotic relations, necessarily, but this one (organelles with eukaryotic cells), which is probably the most ancient and most firmly established of all, seems especially equitable. There is nothing resembling predation, and no pretense of an adversary status on either side" (Thomas, 1974, pp. 86-87).

INTRODUCTION

A EUKARYOTIC cell can be likened to a society composed of a nucleus and a crowd of subcellular organelles in which all members cooperate for the common good. This analogy is more than just a literary device, because the

reproduction of organelles such as mitochondria and chloroplasts is partly independent of that of the nucleus, both within the organism and in the passage from one generation of organisms to the next. Because mitochondria and chloroplasts contain unique DNA molecules which replicate and pass from organelle to organelle, there is a partial uncoupling of the

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reproduction of organelle DNA (oDNA) from that of nuclear DNA (nDNA). Such uncoupling can have important evolutionary consequences since it implies that natural selection acting on the two kinds of DNA will not always favor the same characters. That is, intracellular conflicts of reproductive interest with resulting selection for antagonistic characters may sometimes occur among the members of subcellular societies. This paper explores some possible consequences of such selection on oDNA reproduction.

As described in the excellent review by Grun (1976), DNA is present in both chloroplasts and mitochondria in the form of long, multiple molecules. There is an average of four molecules per mitochondrion in yeast (Grimes, Mahler, and Perlman, 1974), and about twenty molecules per chloroplast in *Chlamydomonas* (Chiang and Sueoka, 1967; Wells and Sager, 1971). In some organisms the molecules seem to be concentrated in a few locations (Ris and Plaut, 1962), but in general their spatial organization is poorly known. The lengths of the molecules vary, but are usually uniform for a given type of organelle in a particular species of organism. Some but probably not all molecules in both types of organelles are in loops, and at least some genetic loci are linked in both chloroplast DNA (ctDNA) and mitochondrial (mtDNA). Probably (with exceptions, see Pring, Levings, Hu, and Timothy, 1977; Dujon, Slonimski, and Weill, 1974) each molecule carries a complete set of organelle genes, at least in mitochondria. Organelle DNA apparently codes for only a small fraction of the compounds that are involved in organelle synthesis and function.

The typical patterns of inheritance of nuclear and organelle genomes during the critical processes of mitosis, meiosis, and fertilization are all different (Fig. 1), and in each process oDNA inheritance is more variable. The patterns of organelle inheritance make possible major intraorganismal heterozygosity in oDNA combined with more or less independent reproduction and transmission of the different oDNA genomes. This situation cannot occur with nDNA. The result is that natural selection acting on oDNA could lead in certain situations to reproductive competition between genetically

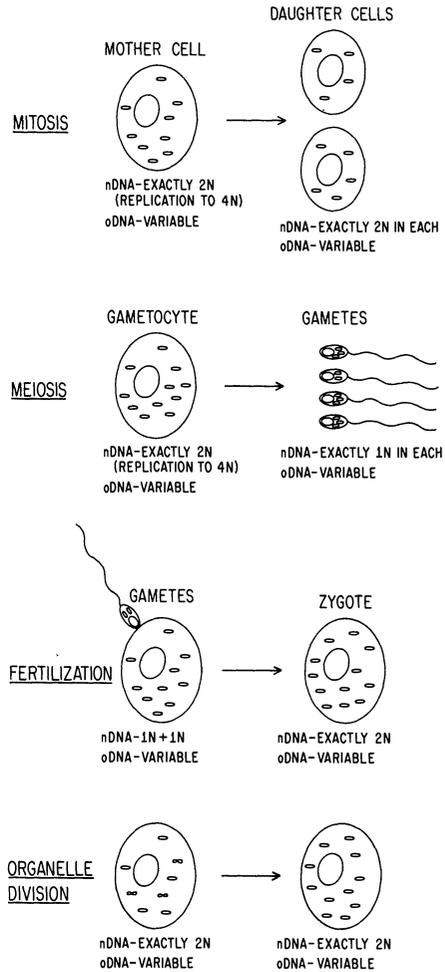


FIG. 1. TYPICAL PATTERNS IN THE CRITICAL PROCESSES OF PROPAGATION OF NUCLEAR DNA (nDNA) AND ORGANELLE DNA (oDNA) WITHIN EUKARYOTIC ORGANISMS

Quantities of DNA are indicated. The nuclear events are highly uniform, whereas those involving organelles are not.

different organelles within a single organism. Another consequence of the inheritance patterns is that some traits which are advantageous for the reproduction of oDNA could be disadvantageous for the reproduction of nDNA, and vice versa, and there could be reproductive competition between oDNA and nDNA. The inheritance patterns could thus give rise to two kinds of intraorganismal conflict (interactions

in which different DNA molecules produce substances to further their own reproduction, at the expense of the reproduction of other DNA varieties in the same organism).

That the symbioses involving organelles in eukaryotic cells may not be as complete as is commonly believed has already been noted by Grun (1976). This paper will attempt to extend this line of thought and (1) to specify both the conditions in which conflict involving organelles might arise and the types of interactions that are expected; (2) to show that these conditions occur in nature and may be common in some organisms; (3) to demonstrate possible cases of the predicted competitive interactions; (4) to show how these ideas may apply to systems other than eukaryotic cells and their organelles, for example, in bacteria and bacterial plasmids, and in animals with endozoic algae; and (5) to compare specific predictions of the theory with available data.

THEORY: SITUATIONS IN WHICH CONFLICT IS EXPECTED

A. *Organelle DNA—Organelle DNA*

Like nDNA genes, varieties of oDNA can compete reproductively by affecting the functioning of the organism in which they are found. For example, promotion of more efficient photosynthesis or ATP production could result in greater reproduction of the whole organism, and thus greater oDNA reproduction (except in some males — see below). In this respect, characteristics which favor the reproduction of oDNA are equally favorable to nDNA reproduction, and cooperative interactions between the two genomes are expected. Such interactions do indeed occur, and reach the point of cooperative synthesis of single compound molecules (e.g., Kung, 1977; Schatz and Mason, 1974). Organelles are vital to the well-being of eukaryotic organisms, and malfunction can mean reproductive death for both oDNA and nDNA.

If, however, there is genetic diversity in the ctDNA or mtDNA within a single organism (i.e., the individual is "heteroplasmic" in the sense of Birky, 1975), then natural selection could favor more direct intraorganismal com-

petition between genetically different organelles for transmission to the next generation. This kind of competition, which would be favored as long as it was not overly damaging to the organism as a whole, could take a variety of forms.

A1. *Selective destruction.* One type of organelle could cause the destruction of genetically different organelles or their DNA.

A2. *Selective inclusion in the embryo.* One type of organelle could cause its own inclusion in or the exclusion of others from the developing embryo.

A3. *Selective inclusion in reproductive structures.* One type of organelle could favor its own inclusion in greater numbers of gametes by selective inclusion in the gonads or gametes (or buds in vegetatively reproducing organisms), by causing gametocytes in which it was present to divide more than others, or by diverting more resources into the part of the organism where it was most common.

A4. *Differential multiplication of organelles.* One type could reproduce more rapidly or inhibit the reproduction of other types, so that its chances of inclusion in gametes were increased.

A5. *Differential DNA replication within organelles.* One of the multiple copies of DNA within a single organelle could reproduce itself or persist better than others.

B. *Organelle DNA—Nuclear DNA*

Under certain conditions, characters favored by selection on oDNA reproduction could be disadvantageous to nDNA reproduction. For instance, natural selection on a character which strongly increased transmission of oDNA from one generation to the next and at the same time slightly decreased the reproduction of the entire organism would be positive for oDNA and negative for nDNA. Such oDNA–nDNA conflict could evolve in the following situations:

B1. *Organelle number in male gametes.* In species in which male gametes are more effective when they are smaller (for example, more easily transported as pollen), selection on nDNA might favor reduction of the number of organelles in the male gametes or even their complete exclusion. Selection on oDNA would obviously favor inclusion of organelles in gametes if such organelles survived in the result-

ing zygotes. If relative numbers of organelles in newly formed zygotes correlated with the relative numbers in that zygote's gametes, selection would also favor the inclusion of as large a number in the gamete as possible.

B2. *Vegetative vs. sexual reproduction.* In species with uniparental maternal inheritance of oDNA, male reproduction by vegetative rather than sexual means would be favored by selection on oDNA, and female vegetative reproduction would be favored in those species with paternal inheritance. The selective forces thought to act on nDNA with respect to sexual vs. asexual reproduction are quite different (Williams, 1975; Maynard Smith, 1978).

B3. *Sex ratio.* In sexual species with strongly uniparental inheritance of oDNA, selection on oDNA could act to bias the sex ratio toward the sex which transmits its oDNA. For example, in a species with maternal inheritance of oDNA and an abundance of sperms available to fertilize each egg, the oDNA in the egg might produce a substance to selectively impede the entrance of those sperms which would result in the zygote becoming male; or, if early death of some embryos caused the mother to dedicate more resources to others, oDNA could reproduce more effectively by selectively killing male zygotes after fertilization had occurred. In hermaphroditic species, male sterility caused by oDNA could be favored if it caused the organism to dedicate more reproductive effort to its female gametes, or if it improved the nDNA constitution of the zygotes formed by female gametes (this is probably often true in plants, as noted by Watson and Caspari, 1960, because of the increased likelihood of outcrossing; see also Lewis, 1941).

B4. *Elimination of nonfunctional organelles.* If a mutation or a sudden change in the environment made a particular type of oDNA in a heteroplasmic organism unable to perform a function important for the well-being of that organism, then selection on nDNA could favor selective elimination of the nonfunctional class of oDNA. Selection on oDNA would oppose such elimination. Selection would be strongest on nDNA when the nonfunctional organelles were especially common or were detrimental to some important cellular function.

B5. *Biparental inheritance with heterosis.* Selection on nDNA could favor biparental inheri-

tance in species in which biparental transmission of oDNA results in heterotic vigor by complementation in zygote organelle function or in recombinant advantage because of the greater variety of oDNA in the offspring. Despite the fact that these advantages would also accrue to the oDNA, selection on oDNA in each gamete would probably often favor elimination of the oDNA derived from the other gamete (A1 or A2 above), because the 50 per cent reduction in reproduction due to dilution (assuming equal contributions of oDNA from the parents) would usually outweigh the heterotic advantages (the same kind of argument is probably sometimes true for nDNA, and results in selection for asexual reproduction; see Williams, 1975). If, however, one parent contributed many more organelles than the other and this difference were maintained throughout the development and reproduction of the zygote, then selection on the organelles in the macrogamete would act only weakly in favor of exclusion of the organelles from the other gamete, and this weak selection might even be outweighed by the advantages of allowing them to enter. The phenomenon of "sorting out" (formation of pure oDNA cell lineages within an organism — see, for example, Birky, 1975) would seem to reduce the probability of heterotic advantage by complementation and recombinational advantage, but it is not clear how rare a type of organelle can be in a heteroplasmic organism and still give heterotic effects.

B6. *Uniparental inheritance with incompatibility.* Selection on oDNA in heteroplasmic organisms might favor relatively more investment of energy and material in replication of organelles or their DNA (e.g., A4 and A5 above) than would be optimal for the efficient performance of organelle functions, or selection might favor a type of organelle that was not completely compatible functionally with the nDNA. In both cases the fitness of the whole organism would be lowered, and selection on nDNA would then favor the reduction of oDNA diversity in the cells of each organism. This reduction of diversity might occur by exclusion of the oDNA of one of the gametes from the zygote, by selective elimination in early development of oDNA derived from one of the parents, or by sorting out the different types of oDNA into different cells.

EVIDENCE

I. Frequency of Occurrence of Conditions in Which Conflict Would Be Expected

[The letters and numbers used in the discussions that follow refer to the sections just above.]

A. Organelle DNA—Organelle DNA

The basic condition for competition between oDNA molecules within an organism is an at least transient heterogeneity of oDNA. How common is this condition in nature? Probably the most common way in which such heterogeneity arises is for a zygote to receive oDNA from both parents. Although inheritance of organelles is usually taken to be maternal, it appears that at least transient biparental inheritance is relatively common. Data come from direct observations of organelles in fusing gametes, and from patterns of inheritance of traits encoded in oDNA. The genetic data are less powerful, however, because only final results are noted, and biparental transmission quickly followed by selective elimination of products from one parent early in embryogenesis is construed as uniparental inheritance.

At least transient or occasional biparental inheritance of chloroplasts has been found in the algae *Zygnema*, *Spirogyra* (Granick, 1961), *Ulva* (Bråten, 1973), *Chlamydomonas* (Sager, 1977), *Hyalotheca* (Potthoff, 1927), and *Rhynchonema* (Chmielevsky, 1890); in the fern, *Scolopendrium* (Tilney-Bassett, 1975); and in the gymnosperms *Pinus* (Mangenot, 1938), *Larix* and *Biota* (Chesnoy and Thomas, 1971), *Chamaecyparis* (Chesnoy, 1973), and *Cryptomeria* (Ohba, Iwakawa, Ohada, and Murai, 1971). (Inheritance in the last four groups is predominantly *paternal*.) In angiosperms, Tilney-Bassett (1975) found genetic evidence of at least occasional biparental inheritance patterns reported in 14 of 38 dicotyledon genera, and in 2 of 10 monocotyledon genera, and he noted that these may be underestimates because of the relative insensitivity of most studies. More recently, biparental patterns have also been found in *Browallia* (Semeniuk, 1976), and in the

monocotyledons *Pennisetum* (Rao and Koduru, 1978) and *Zea mays* (Fleming, 1975). (This last species was listed as uniparental by Tilney-Bassett.)

With respect to mitochondria, conjugation in *Paramecium aurelia* is known to result occasionally in exchange of mitochondria, and the rarer event of fusion produces complete mixing (Adoutte and Beisson, 1972; Beale, Knowles, and Tait, 1972). Sexual reproduction in the fungus *Neurospora* probably also results in mixing of parental mitochondria (Birky, 1975), as does fusion in the yeast *Saccharomyces* (Birky, 1975). Interspecific crosses in the plant *Epilobium* give biparental inheritance (Anton-Lamprecht, 1967). Newly formed zygotes of the gymnosperms *Pinus*, *Larix*, and *Biota* all have mitochondria from both parents, and in the last two species mitochondria from both parents are known to survive in the developing embryo (Chesnoy and Thomas, 1971).

In animals, paternal mitochondria often maintain their structural integrity after penetration of the spermatozoon into the ooplasm (Gresson, 1942; Anderson, 1968). Sperm mitochondria have been seen in electron-microscope (EM) studies of newly formed zygotes of the sea urchins *Arbacia* (Franklin, 1965; Longo and Anderson, 1968) and *Paracentrotus* (Anderson, 1968), the annelid *Hydroides* (Colwin and Colwin, 1961), the hemichordate *Saccoglossus* (Colwin and Colwin, 1963), the trematode *Haematoloechus* (Burton, 1967), the bivalve *Barnea* (Pasteels, 1965), mice and rats (Szollosi, 1965; Presley, 1969), and rabbits (Swift, 1967). As Grun (1976) has noted, if, as is often stated, fertilization generally involves fusion of the sperm plasma membrane with that of the egg, it seems almost inevitable that sperm mitochondria are introduced at least temporarily into most zygotes.

Probably at least temporary transmission of mitochondrial and chloroplast DNA from both parents to the zygote also often results from sexual reproduction by fusion of more or less equal-sized gametes. This type of reproduction is known in many groups of organisms: algae in the Divisions Chlorophyta, Xanthophyta, Pyrrophyta, and Phaeophyta (Coleman, 1962); protozoans in the orders Foraminifera, Euglenoidea, Phytomonadia, Dinoflagellata, Trichomonadida, Hypermastigida, and Gregarina

(Mackinnon and Hawes, 1961); molds such as *Rhizopus* (Simpson and Beck, 1965) and *Alomyces* (Doyle, 1964); and myxomycetes (Bonner, 1974). Conjugation, which involves establishment of cytoplasmic connections between pairs of individuals and probably results at least occasionally in transmission of organelles (e.g., in the case of *Paramecium* above), is widespread in the protozoan class Ciliata (Mackinnon and Hawes, 1961).

Since replication of both mitochondria and chloroplasts is usually stated to be under the control of nuclear genes (see Attardi et al., 1975; Nasyrov, 1978), it might seem that differential reproduction of organelles (A4) would be unlikely. This is probably true inasmuch as nuclear genes code for many organelle constituents, but it does not preclude the possibility that different organelles might multiply at different rates within particular cells. In fact, in *Paramecium*, yeast, and *Neurospora* different mitochondrial mutants have different rates of replication in the same cell (Grun, 1976; Adoutte and Beisson, 1972; Diacumakos, Garnjobst, and Tatum, 1965; Garnjobst, Wilson, and Tatum, 1965; Tatum and Luck, 1967). Coon, Horak, and Dawid (1973) also found gradual changes in frequencies of different types of mtDNA in tissue cultures of hybrid human-rat and human-mouse cells. Schötz (1968) showed that different types of *Oenothera* chloroplast also have different rates of replication which are largely independent of nuclear control.

The importance of selective inclusion in gametes and differential reproduction of organelles (A3 and A4) may be substantially greater in higher plants than in metazoan animals. This is because the primordial germ cells, which will eventually produce the gonads, are usually differentiated very early in animal embryogenesis (Deuchar, 1975); usually only interactions of types A3 and A4, which occur before this differentiation, will have evolutionarily important consequences (exceptions occur — for instance, the mycetocytes which are incorporated into many insect eggs). In plants, on the other hand, reproductive cells are usually dispersed and are differentiated much later. The conditions for selective inclusion in gametes thus occur in many parts of the same organism, and there is more time for differences in organelle reproductive rates to have an effect.

The possibility of differential reproduction of DNA molecules within single organelles depends on several factors, and not enough is known yet to say if these conditions are likely to be common. There must sometimes be differences between DNA molecules within a single organelle which arise from mutations or biparental contributions. Spontaneous mutation rates for organelle genes are stated to range from 6×10^{-4} (Nasyrov, 1978) to 10^{-7} (Beale, Knowles, and Tait, 1972). These values refer to changes in the properties of the entire organelle, however, and their relation to the actual rate of mutation per DNA molecule is not known, since each organelle may contain many DNA molecules. It seems safe to assume that they represent lower limits.

Organelle fusion after biparental transmission of oDNA could also result in intraorganelle heterogeneity. Attardi et al. (1975) imply that fusion may be relatively common for mitochondria, and the fact that crossing over is known in the mitochondrial DNA of yeast, *Neurospora*, and the ciliate, *Tetrahymena* (Birky, 1975), corroborates this. In addition, moving pictures of plant cell mitochondria showed frequent fusion and splitting (Honda, Hongladarum, and Wildman, 1964). Dujon, Slonimski, and Weill (1974) have suggested that the mitochondria of yeast may actually exist "as a dynamic syncytium which continuously fuses and separates." Chloroplasts are generally thought to be less labile, but less is known about the proplastids from which they are derived.

There must also be differential reproduction of different molecules within an organelle. A limited binding site model, which was derived from phenomena associated with bacterial chromosome and perhaps plasmid replication, was proposed by Gillham, Boynton, and Lee (1974), but has not been confirmed. Another possible mechanism would involve different numbers of replication sites on different molecules (H. K. Srivastava, pers. commun.). Chuder and Chiang (1974) also speculated from genetic data that only a fraction of the *Chlamydomonas* ctDNA molecules are "genetically competent," but they offered no mechanism.

The existence in *Zea mays* mitochondria of small pieces of DNA which may become incorporated into nDNA in the manner of episomes

(Pring et al., 1977), and the possibility that the yeast mitochondrial genome may be in two different DNA molecules (Dujon, Slonimski, and Weill, 1974), suggest the possibility of even further complications in the basic scheme presented here.

It is important to note that intraorganelle competition could result in the spread of competitively superior oDNA throughout a cell if organelles do indeed fuse and split frequently, but its spread to other cells would presumably be limited by cell membranes. Thus, in multicellular organisms and especially in animals (see above), the earlier intraorganelle competition were to occur in development, the greater would be its likely effect on that organism's ultimate constitution and the constitution of its gametes.

B. Organelle DNA–Nuclear DNA

B1–4: It is common for gametes of one sex to be much smaller than those of the other and to contain fewer organelles (conditions for conflict involving organelle number in male gametes; also often associated with conditions for vegetative versus sexual reproduction and sex ratio distortion). Small size is often associated with greater motility or ease of transport. Both the fact that residual cytoplasm is shed late in spermatogenesis in many animals (see Turner, 1968), and that in motile plant gametes the nuclei and organelles are tightly packed with little or no cytoplasm surrounding them (e.g., in the charophyte, *Nitella* — Turner, 1968) support the argument that reduced size is advantageous. Uniparental inheritance of organelles is very common (see Grun, 1976). Conditions for conflict that involves elimination of nonfunctional organelles must also occur, at least on occasion, because (a) spontaneous mutations in oDNA are known, and (b) the organelles that are inherited from different parents cannot always be equally functional.

B5 and B6: These conditions are mutually exclusive. Probably heterosis occurs in some organisms, and not in others; it is even possible that within a single species, some oDNA loci give heterotic effects while others give incompatible reactions with nDNA.

It seems clear that in some cases heterosis does not occur, evidently because of incom-

patibility between nDNA and oDNA products. Grun (1976) has listed 20 species in which at least partial sterility is caused by cytoplasmic factors in intraspecific crosses (most crosses were between different races), and many more in which it results from interspecific crosses. From this and other evidence presented by Grun, it seems clear that oDNA and nDNA are sometimes coadapted to each other so that some combinations (not necessarily those likely to occur in nature, however) result in reduced whole-organism fitness. Both Grun and Sager (1975) have argued that maternal inheritance evolved to insure compatibility between oDNA and nDNA.

Hybrid vigor is a widespread phenomenon, however. Combinations of mitochondria isolated from different inbred strains have been shown to have increased oxidation efficiency in wheat (*Triticum* — Sarkissian and Srivastava, 1971), corn (*Zea* — McDaniel and Sarkissian, 1968), barley (*Hordeum* — McDaniel, 1969), and sugar beets (*Beta* — Doney, Theurer, and Wyse, 1972). Although these plants are thought to have maternal inheritance of organelles, at least of chloroplasts (Tilney-Bassett, 1975; see, however, Fleming, 1975), the high correlation between the level of in vitro mitochondrial complementation and the amount of heterotic vigor exhibited by different combinations of inbred strains suggest that the heterosis results from organelle complementation. Heterosis apparently due to mitochondrial complementation has also been seen in the mold *Neurospora* (Pitenger, 1956). Even interspecific and intergeneric combinations of organelles persist and function apparently normally in several kinds of hybrid cells (human, rat, and mouse mitochondria in rat-human and mouse-human hybrid cells in tissue culture — Coon, Horak, and Dawid, 1973; mitochondria from maternal species functioning with nDNA from both parents in horse-donkey and donkey-horse crosses — Hutchinson, Newbold, Polter, and Edgell, 1974; chloroplasts from both parents in tomato-potato hybrids — Melchers, Sacristan, and Holder, 1978, cited by von Wettstein, Poulson, and Holder, 1978). A further argument is that the enzymes responsible for yeast mtDNA recombination seem to be nDNA products that function specifically to promote recombination of mtDNA rather than nDNA (Fraenkel, cited

by Birky, 1975). The implication is that selection on yeast nDNA has favored heterogeneity of oDNA.

There are still other, logical problems with the generality of the incompatibility hypothesis. The male's oDNA is supposedly excluded from the zygote because of the possibility that its inclusion will lower the zygote's fitness owing to its incompatibility with nuclear functions. The nucleus of the zygote, however, is always a combination of both maternal and paternal DNA, and in effect provides a new environment for the oDNA. There is no assurance that in these new conditions the maternal oDNA will function more effectively than the paternal oDNA, and thus no reason to expect that oDNA-nDNA compatibility factors would consistently favor uniparental inheritance. A variation of the incompatibility hypothesis (Grun, 1976) is that maternal inheritance protects the zygote from invasion by reproductively superior but functionally inferior oDNA. The selective advantage in this case would depend on reproductive superiority in oDNA being consistently linked to functional inferiority. Such linkage has not been shown, and may be unlikely if interactions with nDNA like those postulated in B4 indeed occur.

The longer-term heteroplasmic advantage that results from recombinant oDNA in offspring is similar to that postulated for nDNA in sexually reproducing organisms (Williams, 1975). This advantage would appear to be very likely, if one assumes that recombination actually occurs in organelle genomes. Such recombination may be common, because it is known in four of five species for which enough of the organelle genetics is known to be able to detect recombination (chloroplasts in *Chlamydomonas*, Sager and Ramanis, 1970; mitochondria in yeast, *Neurospora*, and the ciliate *Tetrahymena*, but not in mitochondria of *Paramecium*, Birky, 1975). In sum, there are a number of reasons to expect that genetic heterogeneity in oDNA is sometimes advantageous.

II. Observations of Apparent Conflict

A. Organelle DNA—Organelle DNA

Selective destruction (A1): Selective elimination of chloroplasts derived from one of the

parents has been seen in zygotes of the algae *Rhynchonema* (Chmielevsky, 1890), *Spirogyra*, *Zygnema* (Granick, 1961), and *Hyalotheca* (Pott-hoff, 1927). In the alga *Ulva*, the chloroplast from the male gamete is usually (but perhaps not always) eliminated within minutes after zygote formation (Bråten, 1973). The ctDNA from one gamete, but not the rest of the chloroplast, is usually destroyed soon after fusion in the alga *Chlamydomonas* (Sager, 1977).

When yeast cells fuse, the mtDNA from one parent is degraded and replaced by copies of the other parent's mtDNA (Dujon, Slonimski, and Weill, 1974). In the sea urchin *Paracentrotus* the sperm mitochondrion degenerates soon after entering the egg (Anderson, 1968). Sperm mitochondria in the rat are also degraded during embryogenesis (Szollosi, 1965; Presley, 1969), and the same seems to happen with the male mitochondria of the mouse (Presley, 1969) and of *Armandia* (Szollosi in Anderson, 1968). It should be borne in mind that many of these examples are from studies in which the destruction of oDNA in degraded organelles was not confirmed.

Selective inclusion in the embryo (A2): The migration of egg mitochondria to cluster around the egg nucleus, so as to favor their inclusion in the "neocyttoplasm" of the proembryo in the gymnosperms *Larix* and *Pseudotsuga* (Chesnoy and Thomas, 1971), may result from competition for inclusion in the embryo. In at least *Larix* there is reason to believe that the parental organisms may be heteroplasmic for mitochondria (see above).

Selective exclusion of paternally derived mitochondria from the zygote has been seen in the tunicate *Ascidia* (Ursprung and Schabtach, 1965), and of probably both paternal plastids and mitochondria from the embryo in *Pinus pinaster* (Mangenot, 1938) and *P. nigra* (Chesnoy and Thomas, 1971).

The envelopment of the binucleate zygote by pollen-tube cytoplasm (organelles included) effectively excludes nearly all egg organelles from the embryo in the gymnosperm *Biota* (Chesnoy and Thomas, 1971). Selective exclusion may also be the mechanism responsible for the sorting out of different mtDNAs in yeast (Birky, 1975).

Exclusion of pollen organelles from eggs

seems to be common in plants (Granick 1961). It would be interesting, however, to know how commonly occasional exceptions to the uniparental rule occur, since the tiny size and apparent lack of function of the plastids often present in pollen (Heslop-Harrison, 1972) suggest that they have evolved to be transferred. In *Nicotiana tabacum* it has been shown that the chloroplast genome is present unaltered in the tiny plastids in the uninucleate pollen grains, despite the fact that this species shows maternal inheritance of chloroplast DNA (Nilsson-Tillgren and von Wettstein-Knowles, 1970). Tilney-Bassett has noted that "examples of purely maternal inheritance may be due to the failure of male plastids to replicate rather than their failure to enter the egg as is usually assumed" (1973, quoted in Sager, 1975).

Differential multiplication of organelles (A4): As noted above, an apparent case of this type of competition has been seen in *Paramecium* mitochondria (Adoutte and Beisson, 1972). The observation that wild-type mitochondria reproduced either more rapidly or at least as fast as mutants when grown under natural conditions agrees with the prediction that the most rapidly reproducing type should predominate. Beisson, Sainsard, Adoutte, Beale, Knowles, and Tait (1974) also mention this type of competition as a possible explanation for other genetic phenomena in *Paramecium*.

Grun (1976) has argued that competitive interactions are the reason why so few chloroplast mutants have been found after treatment with mutagens in species with several chloroplasts in each cell. The specific form of competition was not specified, but type A4 seems simplest and most likely. The same author argued that "dauermodifications" such as those produced in *Drosophila* by heat treatment may also be due to unequal organelle reproductive rates under different environmental conditions.

Other possible cases include the following. Some "petite" mutations of yeast mitochondria ("suppressive") may reproduce faster than normal mitochondria, and others ("neutral") more slowly (Ephrussi, Margerie-Hottinguer, and Roman, 1955; Ephrussi, Jakob, and Grandchamp, 1966; see, however, Carnevali, Morpurgo, and Tecce, 1969). Chloroplasts from different species of *Oenothera* have differ-

ent rates of multiplication in interspecific crosses (Schötz, 1968). In *Neurospora*, normal mitochondria may outreproduce "poky" mutants, but be in turn slower reproducers than "abnormal-1 and 2" mutants (see Tatum and Luck, 1967). Mutant (white) chloroplasts in the monocotyledon *Pennisetum* may reproduce more rapidly than normal ones (Rao and Koduru, 1978).

Differential DNA replication within organelles (A5): This type of competition was hypothesized by Gillham, Boynton, and Lee (1974) to occur in *Chlamydomonas* chloroplasts. The discovery that inhibition of ctDNA transcription changes inheritance patterns (Sager and Ramanis, 1973) does not fit easily in their model, but it may nevertheless be necessary to take into account interactions between multiple genetic copies in individual chloroplasts to explain the allelic ratios that they report.

Carnevali, Morpurgo, and Tecce (1969) hypothesized that some petite mutations in yeast mtDNA are "suppressive" because mutated molecules replicate faster owing to their apparently shorter length. They cited the study of Mills, Peterson, and Spiegelman (1967) which showed that shorter RNA molecules from an RNA virus reproduced more rapidly in vitro under conditions which favored the survival of more rapid reproducers.

B. Organelle DNA-Nuclear DNA

Sex ratio (B3): E. Charnov has pointed out to me that the apparent alteration of the sex ratio in *Drosophila* by cytoplasmic particles that favor the production of females (Poulson and Sakaguchi, 1961) may represent a conflict between cytoplasmic DNA (in this case spiroplasma organisms which are inherited maternally) and nDNA. Another possible case, described in humans, is a maternally inherited cytoplasmic factor in eggs that is lethal to sperms with Y chromosomes (Leinhart and Vermelin, 1946, in Grun, 1976).

Cytoplasmic factors (mostly not yet associated with specific organelles) cause male sterility in many plant species (18 species in as many genera are listed by Grun, 1976), and pollen sterility is the most commonly observed character induced by such factors (Watson and Caspari, 1960). As predicted by the theory outlined

here, species with this character seem to have maternal inheritance of oDNA: 7 of the 18 species listed by Grun appear also in the list of Tilney-Bassett (1975), and all show strongly maternal inheritance; in addition, two species on the Tilney-Bassett list are in the same genus as an eighth species on the Grun list and also have maternal inheritance. None of the many cytoplasmic male sterility factors in plants is known to be transmitted by pollen (Edwardson, 1970) (this is not a logical impossibility since not all factors cause complete sterility).

Elimination of nonfunctional organelles (B4): Adoutte and Beisson (1972) have shown that in heteroplasmic *Paramecium*, mitochondria which are genetically incapable of functioning in the presence of certain drugs are eliminated selectively when the *Paramecium* is grown in the presence of the drugs. The changes occur within as few as three generations, even when the original mixture of mitochondria (a single organism contains several thousand) is strongly biased toward sensitive mitochondria. Another possible interpretation is that the changes resulted from severe differences in organelle multiplication rates (A4) combined with random degradation.

Advantage and disadvantage from mixing organelles (B5 and B6): In a synthesis of data on *Oenothera*, Stubbe (1963) concluded that the evolution of more rapidly reproducing varieties of chloroplasts has imposed new selective pressures on nDNA because of incompatibility problems, and has in effect been a driving force in the evolution of nDNA in this genus.

If conditions under B5 hold for any of the examples of selective destruction or selective inclusion of organelles in embryos (A1 and A2), then these examples may illustrate oDNA-nDNA conflict in the gametes (generally eggs) of the parent whose oDNA remains intact. In this case, the oDNA of the other gamete may have lost in conflict with this oDNA. If conditions in B6 obtain in any of the cases, then the oDNA in one gamete (the "loser") has lost out in conflict with the oDNA or nDNA of the other.

Other cases, in which biparental inheritance of oDNA occurs, could represent "victories" for nDNA over oDNA in one or both gametes (under conditions in B5), or for oDNA in the male gamete over oDNA or nDNA in the female gamete (under conditions in B6).

OTHER APPLICATIONS OF THE THEORY

There are a number of other situations in nature in which more or less independently reproducing internal entities are bound symbiotically to various organisms (see Henry, 1966; Margulis, 1970). Some of the competitive interactions described here may well occur in these systems also. Two examples will be discussed briefly as illustrations.

Bacterial Plasmids

A great deal is known about these structures, and only a few basic points will be mentioned. These are based on characteristics mentioned in the review by Rowbury (1977).

Bacterial plasmids are extrachromosomal loops of naked DNA that are capable of initiating and regulating their own replication. They are common, but are generally considered non-essential for their host cell; under certain conditions, however, they clearly promote its reproduction. Some "cryptic" plasmids have no known effect on their hosts. Plasmids normally pass from cell to cell during fission and conjugation (transfer), and are occasionally carried by viruses from one bacterium to another (transduction) after incorporation into the bacterial chromosome. Some "transferable" kinds are capable of inducing the host bacterium to initiate conjugation, and thus cause their own propagation to other cells. Others cannot initiate this process, but can be transferred when transferable plasmids induce conjugation. In some conjugations, part or all of the "male" bacterium's chromosome is transferred to the "female," whereas in others only a plasmid or plasmids are transferred. Most (perhaps all) plasmids are capable of being incorporated into the host cell's chromosome. Some can live in more than one species of bacterium.

Considerations of possible direct competition between different plasmids are not straightforward because for many combinations of plasmid types, the presence of one type in a host does not alter the probability of another's being also transmitted to the host's progeny. Their relation to each other is thus somewhat analogous to that between the chloroplasts and mitochondria in eukaryotic cells.

The relationship between some plasmids is

complicated, however, by the fact that the number of plasmids of a given type present in a single host cell is sharply limited (numbers vary from 1 to 50, and are characteristic for each type of plasmid). Presumably as a side-effect of the mechanism responsible for this limitation (still poorly understood), cohabitation of bacterial cells by closely related plasmids is marked by "incompatibility": most daughter cells from a host with a pair of incompatible plasmid types contain only one of the two types. Incompatibility involves inhibition of the replication of one of the types, rather than its destruction or loss. These incompatibility properties are encoded in the plasmid DNA, and all plasmids that are known belong to one of about 20 incompatibility groups. Plasmids of a given group are incompatible with all others of the same group.

Manipulation of incompatibility may be a way in which competition occurs between plasmids. In some cases, when a host cell contains two very closely related plasmid types (recently derived from a common ancestor), the distribution of the two types is about 50:50 in the daughter cells. In other cases, however, one type transmits more copies than the other. Sometimes the "resident" plasmid (the one in the female host prior to conjugation) has a reproductive advantage, while in other combinations one type is consistently transmitted in greater numbers whether it comes from the donor cell or the recipient. This situation may correspond roughly to competition by differential reproduction of organelles (A4).

The phenomenon of "surface exclusion" may be another result of reproductive competition. This property is also encoded in plasmid DNA, and is responsible for reduced genetic transfer between bacteria carrying identical or closely related transferable plasmids. Selection on resident plasmids would favor exclusion of closely related plasmids because they would be incompatible, and thus would reduce the resident's reproduction. This interaction would be similar to exclusion from embryos (A2). The repression of transfer properties of F-like and I-like plasmids by the presence of identical or closely related plasmids could, in the same way, be due to reproductive competition. This repression also results from products encoded in the plasmid DNA.

Another consequence of the incompatibility phenomenon would be that a plasmid type might be favored if it were able to escape incompatibility reactions with others by somehow changing the mechanism by which its numbers were regulated. This could explain the evolution of the number of different incompatibility groups that now exist.

One further plasmid characteristic that may confer a reproductive advantage is ability to induce the host cell to initiate conjugation, since such "transferable" plasmids can thereby spread to other cell lineages. This behavior would correspond to a special case of selective inclusion in gametes (A3), the plasmid itself converting its host into a gamete. Selection on plasmids incapable of inducing conjugation would favor their association with those that could, and would be especially strong in favor of those that were in different compatibility groups from those of the common transferable plasmids.

Evolutionary interactions between plasmids and bacterial chromosomal DNA also may be of interest, but it does not yet seem possible to assess their significance, because of the complication introduced by the occasional inclusion of plasmids in chromosomes, and the lack of understanding of the advantages and disadvantages to the bacterium as a whole of having plasmids present.

Endozoic Algae

Algae of the divisions Chlorophyta and Chrysophyta are known to live in the bodies of a surprisingly wide variety of invertebrates. The list of hosts given in McLaughlin and Zahl (1966) includes 128 genera from 16 classes in 10 phyla. Algae are commonly acquired by the host's ingesting them, at least in the relatively few cases in which the mode of acquisition is known. It would seem that in at least these cases, the chance that a given host would become populated by genetically diverse algae would be high, at least when multiple infection is not rare. Thus, there would be a strong possibility of reproductive competition between the algae within their hosts.

The interactions between host and algal genomes probably run the entire gamut from complete conflict (as in the case of parasitic algae) to complete accord (as in hosts with clones

of algae whose reproduction is completely linked to that of the host).

The work of Siegel (1960) on *Paramecium bursaria* and its endosymbiont *Chlorella* provides a possible example of the elimination of non-functional organelles (B4). When *Paramecium* with algae are kept in darkness, the algae are eventually eliminated. The rate of elimination seems to depend on both the strain of the host and the origin of the algae (presumably algae isolated from different host strains were genetically different); algae persisted longer in those strains from which they were originally cultured. The mechanism of elimination is unknown. Algae from different host strains also reproduce at different rates in different host strains. Still other phenomena, such as the gradual increase of a given algal strain's apparent ability to invade a given host strain may also have evolutionary implications (and at the same time are strikingly similar to the observations made by Beisson et al. (1974) on transfer of mitochondria in *P. aurelia*).

A possible example of competition involving selective inclusion in reproductive structures (A3) occurs in the coral *Pocillopora*, in which algal cells crowd into regions of the host where new buds are being produced (Yonge and Nichols, 1931).

DIFFICULTIES IN TESTING THE THEORY

Ideally a theory's usefulness can be tested by making observations that either confirm or refute its predictions. More precise predictions may become possible when the theory outlined here has been refined and extended, but at the moment it does not seem possible to predict a priori the outcome of any particular conflict situation involving oDNA. This means that the theory suffers from the drawback of seeming to be able to account for any imaginable result. The cases cited above as examples of conflict all have other possible interpretations, and cannot serve as tests.

There do, however, seem to be reasons for expecting some general patterns to emerge. In situations of organelle-organelle conflict such as that between organelles in eggs and sperms, one set of organelles (those of the egg) would seem usually to have an advantage both because

of their superior numbers and also because of the possible accumulation of necessary substrates prior to fertilization. A probable example of this "home-court advantage" comes from interspecific crosses of *Oenothera* (Schötz, 1968). Chloroplasts that are competitively superior owing to their faster replication rates succeed in completely taking over heteroplasmic zygotes when introduced via the female parent, but only partially dominate when introduced by the male. The general prediction is that maternal rather than paternal inheritance would predominate, and this is the case (see Grun, 1976).

Conflicts between oDNA and nDNA are more complex. As oDNA is embedded in a medium largely controlled by nDNA, it would seem that nDNA would have more capacity to insure an outcome favorable to its own reproduction. Leigh (1971, 1977) and Alexander and Borgia (1978) have argued, in the context of nuclear genes acting selfishly against the reproductive interests of the rest of the genome, that the larger group is likely to dominate (they speak of "the power of the collective" in "the parliament of the genes"). Larger genomes would tend to dominate because they have more loci that code for more varied products, and therefore mutations having the effect of suppressing other genomes' detrimental effects would be more likely. Other factors, such as the "suppressibility" of the small genome's actions (which could depend on biochemical details), the amount of product synthesized, and the time elapsed since the detrimental effects first evolved, would also be important. Thus the relative sizes of genomes can give only probable rather than certain predictions of outcomes.

Because yeast mitochondria probably contain about fifty genes (Grimes, Mahler, and Perlman, 1974), and chloroplasts several hundred (Nasyrov, 1977; Wells and Sager, 1971), these organelles may be more likely to succeed in thwarting the interests of nuclear genomes than the single "outlaw" genes discussed by Leigh and by Alexander and Borgia, and yet be less likely to succeed than "outlaw" sex chromosomes which sometimes "murder" one another (White, 1973, in Alexander and Borgia, 1978). By this line of reasoning, bacterial plasmids, which are sometimes as much as about 10 per cent of the size of the host cell's chromosome, would seem even more likely to rebel effectively

than oDNA. If there are cases of quantitative effects on competitive abilities (in which more copies of a genome would increase its chances of prevailing in a conflict) the chances of effective rebellion by oDNA should be improved, since around 10 per cent of a cell's total DNA may be oDNA (Grimes, Mahler, and Perlman, 1974).

It would seem more likely that oDNA could act counter to the selective advantage of nDNA in unicellular organisms than in multicellular ones. This is because the lack of intracellular membranes in unicellular organisms should more readily permit a complete takeover of an organism's set of mitochondria or chloroplasts by "rebel" oDNA by means of any of the following mechanisms: selective organelle destruction, differential organelle reproduction, or differential oDNA reproduction (A1, 4, 5). On the other hand, even complete takeover of a given cell or cells in a multicellular organism (especially animals) would often have no evolutionary consequences for either nDNA or oDNA because of the probable inability of oDNA to move across cell membranes. Unless takeover occurred in cells in the reproductive organs or early in embryogenesis, it would not increase the rate of transmission of oDNA to the next generation, and consequently natural selection would not favor the "rebellious" oDNA. Unfortunately, not enough data are available to test the validity of this prediction of more frequent conflict in unicellular organisms.

Conditions B5 and B6 give opposite predictions, and can only be discriminated by the technically difficult quantification of the factors involved (relative amounts of oDNA passed to the zygote by each gamete; gain in whole-organism fitness from both organelle heterosis and oDNA recombinations; and loss in whole-organism fitness due to intraorganismal competitive interactions or to oDNA-nDNA incompatibility). The balance probably varies in different species. The severity of the incompatibility between oDNA and nDNA would probably often be influenced by the frequencies of incompatible oDNA and nDNA in the population, since selection on both would favor, other things being equal, any variants which were not incompatible. There would thus be a vicious circle similar to the one involving isolating mechanisms during species formation. The

greater the frequency of mixing (formation of organisms with incompatible DNA's), the more likely that alleles suppressing the incompatibility reaction would be present, and render the combination no longer incompatible. If mixing was rare, on the other hand, selection to prevent it would be more likely to prevail. These considerations make it seem likely that continued mixing of incompatible oDNA and nDNA is an unstable condition, and is not likely to be observed frequently under natural conditions. It is even possible that a species with a given balance of selective factors (say, net positive effects from being heteroplasmic) could be descended from an ancestor which had a different balance (say, net negative effects), and could conserve at least vestiges of some characteristics originally evolved in the ancestor. This would make confirmation or refutation of the theory even more difficult.

Given the probable antiquity of nDNA and oDNA interactions (see Uzzell and Spolsky, 1974) and the possibility of changing selective advantages in given evolutionary lines, the control of outcomes would be expected to be variable, and in at least some cases complex, since there would be a coevolution of the two genomes, with each one evolving to produce effects that counteracted those produced by the other. In some cases, however, one genome might win in such a definite manner that selection would cease to favor countermeasures by the other, and control over the outcome could become relatively simple. These lines of reasoning suggest that Sager's (1975) assumption that all organisms have a similar molecular mechanism controlling inheritance of oDNA is wrong.

Finally, it should be noted that although the ideas presented here are obviously related to the theory that chloroplasts and mitochondria evolved from separate endosymbiotic organisms (Margulis, 1970), they are not logically bound to that theory. Even if that theory is wrong, and ctDNA and mtDNA were originally derived from nDNA or plasmids, as soon as these pieces began to be passed from generation to generation in a non-Mendelian fashion, conflict situations would develop, and natural selection would begin to operate on the pieces as separate entities. Thus, neither proof nor disproof of the endosymbiotic theory would serve to resolve the questions raised here.

POSSIBLE TESTS OF THE THEORY

Despite the problems just discussed, three specific predictions can be made:

1. *Direct involvement of oDNA.* In cases of apparent oDNA–oDNA conflict, products transcribed from oDNA rather than nDNA will often be involved in determining the outcome despite the fact that oDNA genes constitute only a small fraction of the total genome (nucleus plus organelles) of the organism.

2. *Antagonistic effects.* There probably exist DNA products whose only effects are to suppress the effects of products of other kinds of DNA in the same organism (oDNA vs. oDNA, oDNA vs. nDNA) in situations in which the effects of the products are in accord with the reproductive advantages of their respective DNA's.

3. *"Unnecessary" complexity and variety.* Mechanisms determining oDNA inheritance will tend to be complex rather than simple, and varied rather than uniform.

It may be premature to test these predictions of biochemical battles within cells, because few species are sufficiently well understood to provide good data. The data available, however, seem to be in accord with the predictions.

Direct Involvement of oDNA

In the alga *Chlamydomonas*, the ctDNA from the "male" gamete is usually selectively eliminated in the zygote (Sager, 1977). Products encoded by the female ctDNA are involved as predicted, since selective inhibition of ctDNA transcription in the female gamete immediately prior to fusion results in biparental or paternal inheritance (Sager and Ramanis, 1973). The final control of ctDNA inheritance is complex, and is also influenced by nDNA. Even in this well-studied species it is not yet fully understood.

The control of inheritance of mitochondria in the yeast *Saccharomyces* is also complex, and not completely understood, but it has been shown that the "polarity" of transmission of markers is determined by the mitochondrial gene ω (Dujon, Slonimski, and Weill, 1974). Polarity evidently involves the destruction of at least a segment of ω^- mtDNA and its replacement with ω^+ mtDNA; it is independent of mat-

ing type. Thus, as predicted, mtDNA is intimately involved in the control of its own inheritance.

Suggestive evidence is available from genetic studies of two higher plants. Interspecific crosses in *Oenothera* show biparental inheritance of chloroplasts, with varying degrees of maternal dominance. Comparisons of the results of crosses that involve different combinations of plastid and nucleus types show that the differential success of transmission of the plastids themselves rather than from differences in the nuclei (Schötz, 1968). These data cannot be taken as conclusive, since interspecific crosses may have had only little evolutionary significance in populations of *Oenothera*, but it is interesting that the plastids do seem to be deeply involved in what appear to be competitive interactions.

In *Pelargonium zonales*, reciprocal crosses between lines with different chloroplast markers frequently produce neither the same nor reciprocal proportions of the markers (Tilney-Bassett, 1975). Tilney-Bassett notes that "Apparently, the plastid contribution from each parent is not simply dependent on the sex difference, but also on whether the plastids are normal or mutant." He goes on to suggest that differences in the transmission between some white mutants (ctDNA) may be due to genetic differences in the chloroplasts. In this species, nDNA also plays an important role in determining ctDNA inheritance. Again the complete mechanism seems to be complex.

The cases of apparent bacterial plasmid competition also seem to accord with Prediction (1), since the products responsible for the outcomes of all the kinds of interaction mentioned are encoded by plasmid DNA, although in a few cases the host cell chromosome may also be involved. This is especially impressive considering the small sizes of plasmid genomes.

There are fragmentary genetic data from *Paramecium* which involve the relative ease of transfer of mtDNA markers between different species ("syngens"), and between individuals which differ in one nuclear locus (*cl*) (Beisson et al., 1974). In some cases the transfer ability ("compatibility") seems to be determined by nDNA, inasmuch as mitochondria can be transferred according to the nucleus of the cell in

which they are grown. The authors suggested that the results could be explained by changes in mitochondrial membrane structure, but it also seems possible that, among other things, they could be attributed to nuclear repression or activation of particular mtDNA genes. In some cases transformation does not occur, a situation which suggests the involvement of mtDNA. Not enough is known yet to judge whether or not Prediction (1) is fulfilled in this species.

Finally, the dramatic electron microscope study of Anderson (1968) suggests that maternal mitochondria are intimately involved in the destruction of the paternal mitochondrion in newly formed zygotes of the sea urchin *Paracentrotus*. The single, large sperm mitochondrion is surrounded by as many as eight egg mitochondria soon after its entry into the interior of the egg. The membranes of sperm and egg organelles become apposed and possibly fused, and the sperm mitochondrion then gradually disintegrates while the egg mitochondria remain intact. Anderson speculated that autolysis was involved, but the physical association of the egg mitochondria with degradation suggests that they are involved as predicted.

Antagonistic Effects

The fact that treatment of female *Chlamydomonas* gametes with ctDNA transcription inhibitor does not result in an even split of inheritance from both parents, but rather in the predominance of paternal genes in zygotes (Sager, 1977) could be explained by the production by male gametes of some substance(s) whose effects, when not counteracted by those of the female gamete chloroplast, act to increase transmission of male ctDNA.

Another possible example is that of the "restorer" alleles which occur in a number of normally hermaphroditic plant species that possess cytoplasmic factors causing male sterility (see above). Most species that have such cytoplasmic factors also have nDNA alleles, called "restorers," which somehow counteract effects of the cytoplasmic factors and cause the plant to revert to male fertility. There are also nuclear genes in *Drosophila paulistorum* which apparently restore male fertility lost due to the action of cytoplasmic spiriplasmas (Ehrman, 1964).

"Unnecessary" Complexity and Variety

The apparent complexity of the mechanisms controlling oDNA inheritance in all five organisms for which sufficient data are available (*Chlamydomonas*, *Saccharomyces*, *Paramecium aurelia*, *Pelargonium zonales*, and *Oenothera* spp.) conforms to this prediction. There does not seem to be any other reason to expect, a priori, that the control of oDNA inheritance should be complex rather than simple.

The mechanisms determining oDNA inheritance also vary widely. As noted above, they include selective destruction of entire organelles, selective destruction of oDNA, physical exclusion of organelles from new embryos, unequal rates of organelle reproduction, and exclusion of organelles from gametes.

CONCLUSIONS

The main objective of this article is to focus attention on the idea that intraorganismal conflict involving organelles may occur, and to apply recent insights in evolutionary thought to subcellular reproductive phenomena. The idea of intraorganismal conflict runs counter to the common conceptions that nucleus-organelle interactions are entirely symbiotic, and that reproductive competition between organelles is evolutionarily unimportant. The change in interpretation is similar to that which has recently occurred with respect to the behavior of individual members of animal societies.

Some of the interactions hypothesized here may never actually occur in nature, and there may well be other kinds of competition that are not listed. Undoubtedly, I have missed many possible examples of competitive interactions already in the literature. Yet, from the data presented here, it seems very likely that *some* kinds of competitive interactions that involve oDNA reproduction do occur, and that organelle biology would be illuminated by perceiving them. The capacities of organelles to control their fates within organisms, as well as the interactions of DNA molecules within organelles, are so imperfectly known that it is not possible to establish clear probabilities for many cases. Although specific hypotheses may be wrong, it is to be hoped that they will serve to

concentrate research effort on heretofore largely neglected critical areas.

In summary, it seems likely that direct reproductive competition between organelles does occur, especially in microorganisms. Organelle-nucleus conflict is also possible, but perhaps less likely (and it is certainly harder to document, because some of the predictions of evolutionary genetics are equivocal). Organelle-nucleus conflict also seems more likely to occur in microorganisms. Competition in multicellular organisms seems especially likely during fertilization and early embryogenesis. It is not yet clear whether or not intraorganelle competition occurs.

Definitive proof or disproof of the existence of some of the postulated interactions may be some time in coming, but the direct involvement of oDNA in determining organelle inheritance seems especially susceptible to experimental testing by treatment of cells with specific oDNA transcription inhibitors, as in the experiments with *Chlamydomonas*. If the theory is correct, many other organisms should show altered

organelle inheritance as a result of such treatment.

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