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On the Dynamics of Symbiote-Dependent Cytoplasmic Incompatibility in Culicine Mosquitoes[1]

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The population dynamics of cytoplasmic incompatibility in culicine mosquitoes is discussed in the context of recent discoveries of the biological basis of this phenomenon. A simple model is derived for predicting prevalence rates of infection with cytoplasmic incompatibility factors over successive generations of a host species. Equilibrium prevalence rates are also predicted. It is pointed out that an incompatibility between carrier males and noncarrier females allows the maintenance of detrimental, i.e., parasitic, infectious agents within a population by maternal inheritance alone. Several of the model's predictions should be testable in population cage experiments.

KEY WORDS: *Culex pipiens; Wolbachia pipientis*; cytoplasmic inheritance; cytoplasmic incompatibility condition; symbiosis; population dynamics.

INTRODUCTION

"Cytoplasmic incompatibility," defined as a functional incompatibility between a cytoplasmic milieu (mainly maternally inherited) and some introduced (thus typically of male origin) chromosomal or extrachromosomal factor, is a widespread phenomenon in nature. Among the better known examples are the cytoplasmic pollen sterility of corn and other grains (Rhoades, 1933; Duvick, 1965), the maternally inherited "sex ratio" and male sterility factors of several species of *Drosophila* (Magni, 1953; Poulson, 1963; Ehrman and Kernaghan, 1971), and the cytoplasmically determined infertility observed in crosses between strains of mosquitoes within the *Culex pipiens* (Laven, 1956; Yen and Barr, 1974) and *Aedes scutellaris* (Yen, 1975) species complexes.

In each of these examples, the cause of the incompatibility is a self-replicating extrachromosomal factor. In several of them, the responsible factor has been identified as an infectious agent, or symbiote, bearing affinities to one or another group of microorganisms: the spirochetes of *Drosophila willistoni* and *D. pseudoobscura* (Poulson, 1963), the "mycoplasma-like organisms" of *Drosophila paulistorum* (Ehrman and Kernaghan, 1971), and the rickettsial *Wolbachia* agents in culicine mosquitoes (Yen and Barr, 1973). Though some of these agents, for example, the spirochetes of *Drosophila*, can be transferred between hosts by laboratory inoculation, it is thought that such horizontal transfer does not occur in nature, and that these agents are totally dependent upon vertical (hereditary) transmission for their maintenance in wild populations. Indeed, one could argue that some of these agents are so intimately associated with host tissue as to challenge the distinction between infectious agents and cell organelles.

It is tempting to search for analogies between these several examples of cytoplasmic incompatibility. In one sense, each seems to share a common feature: The presence of the agent or factor is selectively detrimental to carrier males, either to male organs (as in hermaphrodite plant species)

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or to male individuals (as in the *Drosophila* examples) or by rendering infertile crosses between carrier males and noncarrier females (as in culicine mosquitoes). But, beyond this similarity, the population dynamics of each of these cytoplasmic agents is unique, due to special interrelationships with chromosomal genes and to the varied natures of the effects upon the host. The major contribution to our understanding of the dynamics of such systems has been made by Caspari and Watson in theoretical studies on cytoplasmic sterility in mosquitoes (Caspari and Watson, 1959), on cytoplasmic pollen sterility (Watson and Caspari, 1960), and on cytoplasmic "sex ratio" conditions in *Drosophila* (Watson, 1960). In this important series of papers the authors developed a set of models describing the dynamics and equilibria states of several types of cytoplasmic incompatibility phenomena, based upon simple but reasonable assumptions.

Recent years have witnessed increased interest in the cytoplasmic incompatibility condition found in mosquitoes of the *Culex pipiens* complex, stimulated by the recognition that this condition might be manipulated for the "genetical" control of these important disease vectors (Laven, 1967a; Curtis and Adak, 1974). Among the fruits of this research have been several discoveries with significant implications for the dynamics of such incompatibility factors in wild populations. The most important of these are: (1) the recognition that incompatibility among *C. pipiens* mosquitoes is due to the presence of rickettsial agents, *Wolbachia pipientis*, within certain cells of the hosts (Yen and Barr, 1973); (2) the discovery that, in reciprocal crosses between infected and uninfected strains, it is only the uninfected female × infected male cross which is incompatible (Yen and Barr, 1973); and (3) the recognition that males may lose their incompatibility with increasing age (Singh et al., 1976; Subbarao et al., 1977). The implications of these three findings, which imply a situation somewhat beyond the boundaries of the basic assumptions of Caspari and Watson (1959), are discussed below.

THE CYTOPLASMIC INCOMPATIBILITY PHENOMENON IN *Culex pipiens*

Within most interbreeding populations of *C. pipiens* mosquitoes, most if not all individuals of both sexes are infected with *Wolbachia*. These rickettsiae are found primarily in the cytoplasm of certain cells in gonadal tissue and are apparently passed on from cell to cell as part of the cytoplasm allocated to daughter cells at cytokinesis. Whether the allocation of these agents is by a random sorting out process or is controlled by some mechanism analogous to mitosis is not known. However, it would seem reasonable to assume that there is at least a finite probability ($P > 0$) that an oocyte or spermatocyte produced by an infected mosquito will carry no *Wolbachia* at all. Studies by Yen and Barr (1973) on aposymbiotic mosquitoes suggest that such uninfected oocytes or spermatocytes should be viable.

Whatever the mechanism of cell and tissue allocation, it appears that most mature ova produced by infected females do contain large numbers of the symbiotes. In males, on the other hand, although most early spermatocytes of infected individuals contain *Wolbachia*, the symbiotes appear to be absent from mature spermatids. It is probable that the *Wolbachia* are lost by a sorting-out process early in spermiogenesis, or else are shed with the cytoplasm bleb during late spermiogenesis. Just how and when this loss of *Wolbachia* occurs is not clear, though recent work on the "partial incompatibility" of older males suggests that it may be an event of some importance (Singh et al., 1976; Subbarao et al., 1977). It appears that some spermatids of older infected males behave like spermatids from uninfected males, perhaps because the density of *Wolbachia* per cell is progressively reduced in successive cell divisions in spermatogonial tissue. Whether the effect of the *Wolbachia* upon sperm is dependent upon the presence of certain numbers of

symbiotes at a certain "critical" stage in sperm development is not clear, but such an hypothesis is consistent with current evidence for the loss of incompatibility in older males.

The implications of the infection status of gametes are illustrated in Figure 1. The solid black symbols in this diagram represent infected individuals or gametes. The stippled cartoon of a spermatid represents sperm which, though they may lack *Wolbachia* per se, have at least been affected by them during their ontogeny. The open symbols represent individuals or gametes which behave as though they were totally uninfected. It will be noted that all fertilizations are compatible except for those between affected (stippled) sperm and uninfected ova. Experimental evidence for this scheme is found in the work of Yen and Barr (1973).

Different geographical populations of *C. pipiens* are thought to behave, within themselves, as described above. But crosses between such populations may also prove incompatible. These patterns of incompatibility are complex, sometimes being reciprocal, but usually not, e.g., Laven (1969). A current explanation for this phenomenon attributes these crossing patterns to different "incompatible" strains of *Wolbachia* which have arisen in different populations. It has been suggested that they may have played a major role in the subspeciation process within the *C. pipiens* complex (Laven, 1967b), though the analysis by Caspari and Watson (1959) suggests that unidirectional incompatibility could lead to divergent evolution only if the populations were isolated.

We concern ourselves here not with the relationship between different populations of infected mosquitoes, but with the problem of the maintenance of infection within a single population.

MODEL FOR THE MAINTENANCE OF *Wolbachia pipientis*

The above description of the natural history of *W. pipientis* can be expressed in terms appropriate for quantitative analysis. The terminology and formulation presented here are consistent with a general vertical transmission model developed by Fine (1975), and will be shown to be an extension of the treatment by Caspari and Watson (1959). We begin by defining five parameters.

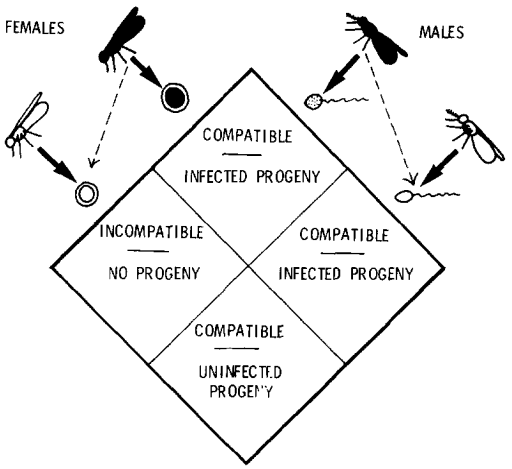

FIG. 1. Diagram showing the results of different mating combinations within a *Culex pipiens* population. Shaded individuals and ova are infected with *Wolbachia pipientis*. Stippled spermatid was affected by *Wolbachia* at the critical period in its spermiogenesis. Open individuals and gametes are, or behave as though they were, uninfected.

B_a: The prevalence rate of *W. pipientis* infections within a randomly mating population of adult *Culex pipiens* mosquitoes. We assume that the prevalence rate is similar among males and females. Present evidence suggests that this prevalence rate is extremely high in wild populations.

d: Maternal vertical transmission rate, i.e., the proportion infected among the ova produced by infected females. This too is thought to be extremely high in natural populations.[3]

w: Paternal gamete "affection" rate, i.e., the proportion affected among the sperm produced by infected males. As noted above, it is thought that *mature* sperm do *not* actually carry *Wol-*

[3] In an earlier publication (Fine, 1975), the author used the symbol r for this maternal vertical transmission rate parameter. This led to some confusion because of that symbol's traditional association with either the recovery rates or intrinsic rates of natural increase. The d symbol used here is consistent with the notation of Heritier (1970).

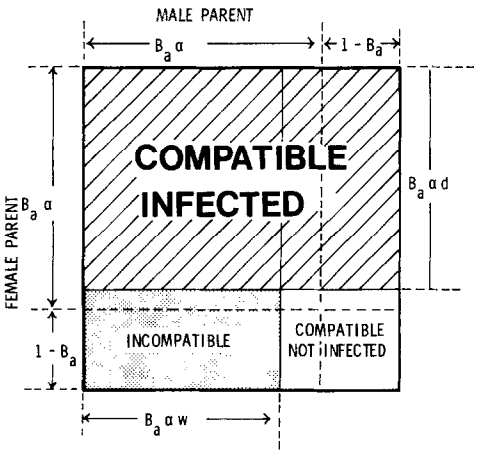

FIG. 2. Venn diagram illustrating the relative proportions of compatible infected, compatible noninfected, and incompatible zygotes produced by a randomly mating population of *Culex pipiens*. The prevalence rate of *Wolbachia pipientis* infections among adults is B_a.

bachia, but that the crucial factor in the incompatibility relationship is whether or not a spermatid was infected up to a certain functionally defined stage in its maturation. The w parameter thus refers to the proportion of sperm produced by an infected male which are affected by *Wolbachia* at that critical period in their genesis.

α: Relative fertility rate, i.e., the relative number of successful zygotes, produced by an infected individual (male or female, we assume any fertility effect of the *Wolbachia* to be independent of sex) as compared to an uninfected individual.

β: Relative survival rate, i.e., the relative survival rate, from hatching to reproductive majority, of infected as compared with uninfected individuals (once again, we assume no sex difference in the effect of the infection).

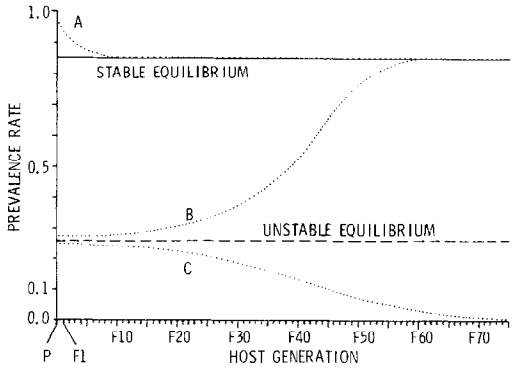

FIG. 3. Diagram illustrating trends in prevalence rates of an infection causing a *C. pipiens*-type cytoplasmic incompatibility in successive generations of hosts. Graph presents repeated solutions of Eq. (1), with $\alpha = 1.0$, $\beta = 1.0$, $d = 0.9$, and $w = 0.5$. Initial prevalence rates were set at $B_a = 1.0$ (line A), $B_a = 0.27$ (line B), and $B_a = 0.25$ (line C).

The subsequent argument can be demonstrated diagrammatically, as in Figure 2 (see Fine, 1975, for further discussion of this method). A square Venn diagram is constructed so as to represent the parentage of newly hatched individuals. The status of female parents is represented along the vertical side and that of the males along the horizontal. If a proportion B_a of the females are infected, and these individuals have, on the average, α times as many progeny as do uninfected individuals, then the proportion of *all* progeny which come from infected mothers must be equal to $B_a\alpha/(1 - B_a + B_a\alpha)$. This proportional distance is measured along the vertical axis and is reflected across the area of the Venn square. But only a proportion d of the ova produced by infected females actually receive the *Wolbachia* from them; and, thus, the total proportion of ova which carry the agent should be: $B_a\alpha d/(1 - B_a + B_a\alpha)$. The corresponding area is shown as diagonally hatched in Figure 2.

Precisely the same argument applies to males, with the substitution of w for d. Note that the proportion $B_a\alpha w/(1 - B_a + B_a\alpha)$ refers to the proportion of mature sperm, produced by an infected male, which were "affected" at the critical stage in their spermiogenesis.

Inspection of the diagram informs us of the relative proportions of presumptive zygotes with different parentage. According to our current understanding of the mechanism of incompatibility in mosquitoes, those presumptive zygotes which comprise an uninfected female gamete and an affected male gamete do not develop. The area corresponding to these incompatible fertilizations is identified by heavy shading

in Figure 2. The remaining combinations should be viable. By comparing the region with diagonal hatching to the area corresponding to all viable progeny, we can define the proportion infected among all viable progeny as:

$$\frac{B_a\alpha d(1 - B_a + B_a\alpha)}{B_a\alpha d(1 - B_a + B_a\alpha) + (1 - B_a + B_a\alpha - B_a\alpha w)(1 - B_a + B_a\alpha - B_a\alpha d)}.$$

Then, by defining B'_a as the prevalence rate of infection among adults of the F_1 generation, and by allowing for differential survival between infected and uninfected individuals as per the definition of β, we have:

$$B'_a = \frac{\beta B_a\alpha d(1 - B_a + B_a\alpha)}{\beta B_a\alpha d(1 - B_a + B_a\alpha) + (1 - B_a + B_a\alpha - B_a\alpha w)(1 - B_a + B_a\alpha - B_a\alpha d)}. \quad (1)$$

Any set of B_a, α, β, d, and w, values may be substituted into this expression in order to predict the expected prevalence rate of infection among adults of the next generation. We now explore the implications of this expression for the dynamics of cytoplasmic incompatibility in culicine mosquito populations.

IMPLICATION FOR THE DYNAMICS OF CYTOPLASMIC INCOMPATIBILITY

1. By reiterative solution of expression (1), we can predict the prevalence rate of infection in successive host generations, given any initial prevalence rate B_a and any set of α, β, d, and w parameters. A set of such solutions is illustrated in Figure 3, showing the predicted course of an infection over successive generations on the assumption that $\alpha = 1$, $\beta = 1$, $d = 0.9$, and $w = 0.5$. Three different solutions are shown, based on different initial prevalence rates B_a. It is clear that these parameter values are consistent with a stable equilibrium prevalence rate at approximately $B_a = 0.85$. An unstable equilibrium exists at approximately $B_a = 0.26$, below which prevalence rates decrease irrevocably toward zero, and above which the prevalence rate rises toward the stable equilibrium level.

2. The existence of equilibrium prevalence rates may be explored directly, by substituting $B_a = B_a'$ into expression (1) and solving for B_a. The following quadratic equation is obtained:

$$B_a^2[\alpha\beta d(\alpha - 1) + \alpha^2(1 - d - w + dw) + \alpha(d + w - 2) + 1] + B_a[\alpha\beta d(2 - \alpha) + \alpha(2 - d - w) - 2] + 1 - \alpha\beta d = 0. \quad (2)$$

Any set of α, β, d, and w values may be substituted into Eq. (2). If they are competent for long-term maintenance of the cytoplasmic agent within the population, there will be at least one root $0 < B_a \leq 1$. The stability of such roots is easily explored by substituting the parameters into Eq. 1 and then noting the behavior of the prevalence rate in subsequent generations if assigned an initial value slightly greater or slightly less than the equilibrium root.

The nature of such equilibria can be illustrated graphically using a convention described by Watson (1960) and shown in Figure 4. The curved lines in these graphs are determined by the values of the α, β, d, and w parameters and show the relationship between parental and filial generation prevalence rates which should occur over the full possible range $0 \rightarrow B_a \rightarrow 1$. The diagram in Figure 4a describes the same conditions as illustrated in Figure 3. The parameter set is seen to be consistent with two equilibrium values: a stable level at approximately $B_a = 0.85$ and an unstable one at approximately $B_a = 0.26$. Provided

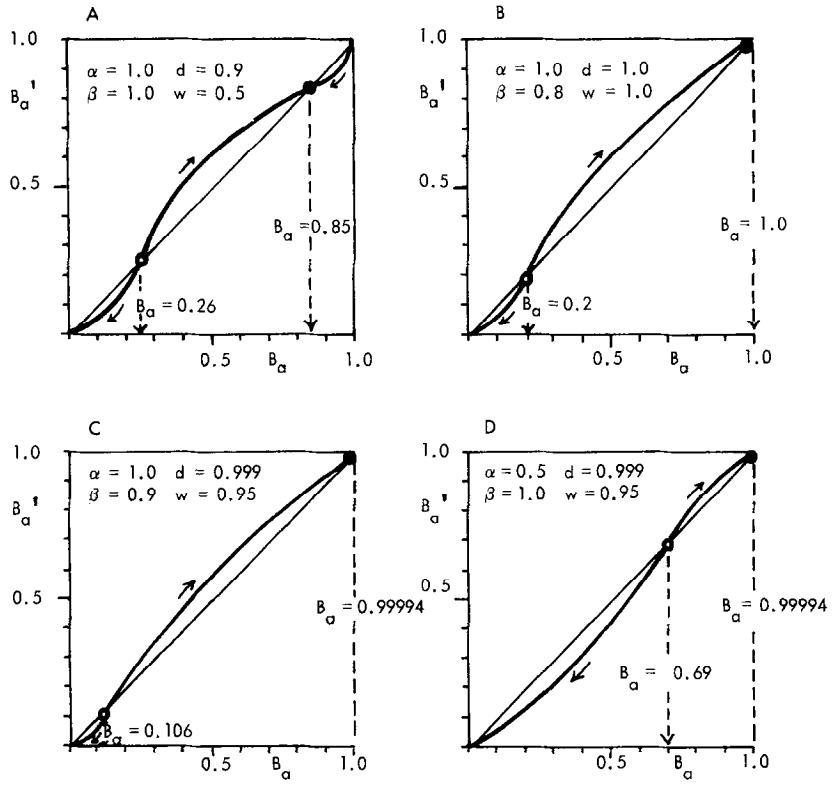

FIG. 4. Diagrammatic representation of the relationship between prevalence rates in successive generations ($B_a \rightarrow B_a'$), as predicted by Eq. (1), for four different sets of α, β, d and w. The line $B_a = B_a'$ represents equilibrium frequencies. Points above this line ($B_a' > B_a$) indicate increasing prevalence rates. Points below the line ($B_a' < B_a$) indicate a falling prevalence rate. Solid circles symbolize stable equilibria; open circles indicate unstable equilibria. Graph A represents the same conditions as illustrated in Figure 3. Graph B duplicates Caspari and Watson's (1959) limiting condition model. Graph C illustrates that vertical transmission rates such as are found in nature can maintain infections which impair the survival of their hosts ($\beta < 1.0$). Graph D presents conditions of symbiote-dependent fertility depression ($\alpha < 1.0$), as implied in the data of Yen and Barr (1973, 1974).

that the initial prevalence rate of infection in such a population was greater than 0.26, it should rise and stabilize at approximately 0.85. But, if the initial prevalence rate was less than 0.26, the infection should disappear progressively from the host population, as indicated by line C in Figure 3.

3. It is of interest to investigate whether a cytoplasmic agent which is detrimental to its host (e.g., $\alpha\ \beta < 1$) can be maintained by this incompatibility mechanism. One way to explore this relationship is to investigate the condition $\alpha = \beta = 1$, corresponding to the case in which the cytoplasmic factor is a commensal with no effect upon its host's gamete production or survival potential. Substitution of $\alpha = \beta = 1$ into Eq. (2) leads directly to:

$$B_a^2 dw - B_a w + 1 - d = 0. \qquad (3)$$

In order for this equation to have at least one root $0 < B_a \leq 1$, the following conditions must be upheld: $d \geq 0.5$, and $w \geq 4d(1 - d)$. The range of minimal d and w values consistent with maintenance of a commensal is shown by the heavy line in Figure 5. Any combination of values to the right of this line, such that $d > 0.5$ and $w > 4d(1 - d)$, has more than enough potential to maintain a commensal and would

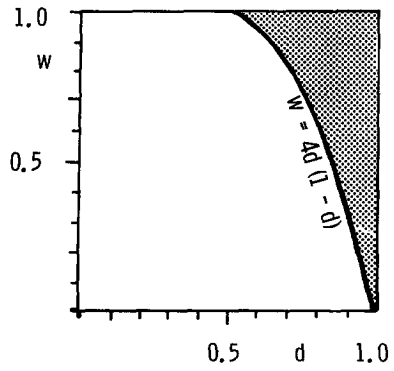

FIG. 5. Diagram illustrating minimum combinations of the maternal vertical transmission rate (d) and the paternal gamete "affection" rate (w) capable of supporting a commensal factor ($\alpha = 1.0$, $\beta = 1.0$) by the cytoplasmic incompatibility mechanism shown in Figure 1. Heavy line represents the threshold $w = 4d(1 - d)$, $d > 0.5$. Combinations of d and w within the shaded region of the figure are capable of supporting cytoplasmic factors with at least a limited detrimental effect upon the host ($\alpha\ \beta < 1.0$).

be sufficient to maintain agents which have at least a limited detrimental effect upon their hosts, i.e., $\alpha\ \beta < 1$.

DISCUSSION

The model described here is similar to but more general than that developed by Caspari and Watson (1959). In essence, their model represents a limiting condition of the scheme presented here: the condition $\alpha = 1.0$, $d = 1.0$, and $w = 1.0$. The earlier model was developed before recognition of the rickettsial etiology of the incompatibility phenomenon. Thus, Caspari and Watson (1959) labeled their two mosquito types as "a" and "b," so that the cross "b" female × "a" male was incompatible. Mosquitoes of their type "a" thus correspond with infected individuals in the present analysis.

Caspari and Watson (1959) concluded that, in the absence of any selective advantage or disadvantage (i.e., $\alpha = \beta = 1$), the prevalence rate of "a" (infected) mosquitoes will increase to fixation. Their result is duplicated precisely by the substitution of $\alpha = \beta = d = w = 1.0$ into Eq. (1). The results of the two models are then algebraically identical. Caspari and Watson (1959) further noted that the "b" (uninfected) type could only be maintained in a randomly mixing population if such individuals enjoyed a selective advantage $S = 1/\beta > 1.0$ over the "a" (infected) types. Their prediction is duplicated by substituting $\alpha = d = w = 1$ into Eq. 2 and solving for B_a. The two roots obtained are $B_a = 1$ and $B_a = 1 - \beta$. As pointed out by Caspari and Watson (1959) and as illustrated in Figure 4b, the equilibrium $B_a = 1 - \beta$ is unstable. According to these assumptions ($\alpha = 1$, $d = 1$, $w = 1$), therefore, the prevalence rate of infected mosquitoes should ultimately converge toward either zero or unity.

The recent discoveries of the particulate nature of the cytoplasmic incompatibility factor, of the viability of individuals lacking the etiological factor, and of the loss of incompatibility in older infected males all imply that the limiting assumption $d = 1$ and $w = 1$ may not be correct. The true maternal rate d may be only slightly less than unity, e.g., 0.999, but the paternal rate w is probably appreciably less than this.

It is now known that the efficiency of gamete infection by *Wolbachia* decreases with age of male mosquitoes. There may be a similar variation in females as well. Epidemiological analyses such as described here require that these age variations be taken into account. The net paternal gamete "affection" rate should thus be calculated as $w = \sum l_x f_x w_x / \sum l_x f_x$, where l_x and f_x are the standard life-table symbols for the probability of survival to age x, and the age-x specific fertility rate, respectively. The w_x here stands for the paternal gamete "affection" rate of males at age x. The corresponding net maternal vertical transmission rate would be $d = \sum l_x f_x \delta_x / \sum l_x f_x$, where δ_x corresponds to the age-specific maternal vertical transmission rate (Fine and Sylvester, 1977).

Once calculated, these net vertical trans-

mission rates may be substituted into expressions (1) and (2) in order to assess their implications for the total epidemiological situation. For example, if the net vertical transmission rates were found to be $d = 0.999$ and $w = 0.95$ (these estimates do not seem unreasonable on the basis of current information), we find that cytoplasmic infections which are detrimental to their individuals' hosts (e.g., $\alpha\ \beta < 1$) could still be maintained in perpetuity in the population. A case in point is provided by the parameter set $\alpha = 1$, $\beta = 0.9$, $d = 0.999$, $w = 0.95$, which is illustrated in Figure 4c. The stable equilibrium prevalence rate under such conditions would be approximately $B_a = 0.999942$. Such might well be the situation within some populations of *C. pipiens* complex mosquitoes in nature. Testing such a prediction would be difficult, as the estimated prevalence rate is virtually indistinguishable from unity. On the other hand, it might be feasible to test the estimated unstable equilibrium point ($B_a = 0.11$, in this case) in population cage experiments, by noting whether the prevalence rate would rise or decline depending upon its initial value near this estimated breakpoint threshold.

In order to use this model to predict equilibrium prevalence rates of infection with cytoplasmic incompatibility factors, it is necessary to have prior information as to the effect of the infection upon host survival (β) and fertility (α). Such data should be readily obtainable through comparisons of symbiotic and aposymbiotic individuals in similar environments (Fine and Sylvester, 1977). Unfortunately, there are almost no data on these parameters in the current literature. The only exceptions are some figures on egg raft size and hatchability presented in Table 5 of Yen and Barr (1973), Table 2 of Yen and Barr (1974), and Table 1 of Yen (1975). These data suggest that aposymbiotic females may deposit larger egg rafts (56.3 and 64.4 eggs/raft, from Yen and Barr's strains 1A and 3A, respectively) than do symbiote-infected females of the original strains (42.6 and 44.2 eggs/raft, for strains 1 and 3, respectively). In addition, the proportion of eggs hatching was higher from aposymbiotic females (0.524 and 0.738, for strains 1A and 3A) than from the original symbiote-infected strains (0.221 and 0.502, for strains 1 and 3, respectively). These data must be interpreted with extreme caution, especially as the fertility of control symbiote-infected crosses was surprisingly low. Nevertheless, they are the only data available and do suggest that *Wolbachia* infection might depress the fertility of the mosquito host. In order to explore the implications of symbiote-dependent depression of fertility, the parameter set $\alpha = 0.5$, $\beta = 1.0$, $d = 0.999$, $w = 0.95$ was substituted into expression (1), and the result is illustrated in Figure 4d. A very high unstable equilibrium frequency at approximately $B_a = 0.69$ is indicated, in addition to the stable equilibrium prevalence rate near unity. It should be possible to test such a prediction in population cage experiments.

These latter results illustrate an extremely interesting and important point with regard to the cytoplasmic incompatibility phenomenon as found in *C. pipiens* complex mosquitoes. This mechanism may be capable of maintaining infections which are deleterious to infected individuals ($\alpha\ \beta < 1$) by vertical transmission alone. This is possible despite the fact that hereditary transfer of the agents is solely matroclinal, and even though the maternal vertical transmission rate and the paternal gamete affection rate are less than unity ($d < 1.0$, $w < 1.0$).

The mechanism for this maintenance should be intuitively clear. As is usual in cases of cytoplasmic incompatibility, it is the cross female (−) × male (+) which is inviable or infertile: hence, the presence of infected males in a population will lower the average fertility of any uninfected females present. Thus, selection against uninfected females is dependent

upon the frequency of infected males in the population. And, since females are largely responsible for the intergeneration transfer of cytoplasmic material, this relative disadvantage associated with the uninfected status in females can counteract a tendency for cytoplasmic factors to be lost from the host population because of inefficiencies in their inheritance mechanism, e.g., $d < 1.0$.

It remains to point out that this analysis is analogous, but not identical, to the general vertical transmission model described by Fine (1975). The assumptions of that general model do not apply when there is a unidirectional symbiote-dependent incompatibility. Thus, both of these models, along with those of Caspari and Watson (1959), remain separate but complementary in their roles as analyses of fundamentally different kinds of Type II-a vertical transmission phenomena (Fine, 1975).

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