

Chromosome Rearrangements for the Control of Insect Pests

Natural populations of insect pests could be displaced by strains bearing compound chromosomes.

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For several years some biologists have been interested in the possibilities of employing genetic techniques in the control of insect pests. One idea has been to introduce in the natural population genotypes which could subsequently facilitate control, or which might render the pest innocuous. Another idea that followed from the success of the "sterile male" technique was to release genotypes with chromosomal aberrations whose subsequent segregation would result in sterility effects damaging to the population. Whitten (1) suggested combining these two ideas in one operation: in its simplest form the desired genotype would be obtained by incorporating the required genes in a chromosomal translocation. This would then be released as a homozygote in excess of the intrinsic unstable equilibrium which would result from the semisterility of the translocation heterozygote. The translocation producing the desired genotype would then autonomously become fixed while the genotype at the same time would produce sterile progeny in the early stages of the process. Thus we have the concept of a genetic transporting mechanism and a desired genotype to be transported, with the additional benefit of a transport device that might itself have transient damaging effects.

In this article we review some of the more general aspects of this concept, and then we discuss in some detail a special kind of translocation called a compound chromosome (or pseudo isochromosome), which could be used as a transporting device.

Two kinds of desired genotypes may be introduced: (i) those rendering a

population vulnerable to subsequent control methods, for example, a genotype carrying a conditional lethal gene, and (ii) those nullifying the noxious characteristics of the pest and thus making control unnecessary.

Genetically determined characteristics of the first kind of genotype already exist or could be readily synthesized in a number of important pest species. For example, susceptibility to insecticides can generally still be utilized even though resistance to that insecticide might be widespread in the species concerned. Sensitivity to either high or low temperatures could be useful in controlling multivoltine species (1, 2). Such sensitivity occurs naturally in geographical races or is inducible with mutagens (2).

The second kind of genotype desirable for introduction is well exemplified by vectors of disease, where a satisfactory solution would be the interruption of disease transmission by the replacement of vector (susceptible) forms of the species by non-vector (refractory) varieties (3). Vector capacity is under genetic control and some vector species are polymorphic for susceptibility (4) so that here our objective would be to increase to the point of fixation a genotype that already occurs in the pest population.

It is reasonable to assume that if these two kinds of desired genotype were simply released in a population without the aid of a transport mechanism they would, in most instances, be quickly rejected by natural selection. For strains synthesized in the laboratory, one might expect the new genotypes to have deleterious side effects on Darwinian fitness, not only because of pleiotropy, but also because the strains would be synthesized on a background naturally selected for laboratory rather

than field conditions. Even with species polymorphic for susceptibility it is possible that the polymorphism would be stable and be naturally restored subsequent to a release.

Two kinds of transporting mechanisms have been suggested: (i) "meiotic drive," where heterozygotes for a particular chromosome are caused to transmit that chromosome in more than the usual 50 percent of the gametes (5), and (ii) genetic situations in which negative heterosis (underdominance) leads to elimination of one or the other homotype (1). The movement in the latter system away from an intermediate unstable equilibrium provides the transporting force.

Discussion in detail of the first type of transport mechanism is beyond the scope of this article. For the second type, homozygous reciprocal translocations (1, 6), pericentric inversions, and compound chromosomes (see later) are all formal possibilities, since heterokaryotypes of these with the "normal" arrangements would have the lowest fitness, because of either sterility or lethality. Reciprocal cytoplasmic incompatibility (3) is another possible mechanism for at least one mosquito vector, *Culex fatigans*. These examples produce the classical dynamics of negative heterosis and are fundamentally different from meiotic drive. Whereas meiotic drive is unidirectional, the frequencies of these aberrations will move in either direction away from an unstable equilibrium point.

If the chromosomes of the released strain were sufficiently rearranged to make the hybrid between it and the field strain virtually sterile, displacement could occur in as few as six generations (1). By means of homozygous reciprocal translocations, this amount of rearrangement might be attained with some insects, such as the higher Diptera, but with the important group of disease vectors, namely the mosquitoes, too few chromosomes ($2n = 6$) might make that amount of rearrangement impossible and prevent synthesis of an adequately complexed strain for release (7).

A critical requirement is that there must be virtually complete linkage of the desired genotype with the transporting mechanism. This is clearly a problem with meiotic drive. In the case of chromosomal aberrations, single translocations or inversions could allow considerable leakage from the chromosome pool of the wild strain although the virtual sterility of strains with multiple translocations may effec-

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tively prevent such recombination. With compound chromosomes, the subject of the remainder of this article, complete genetic linkage is probable because all hybrids between a strain carrying such a chromosome and a structurally wild-type strain die as embryos. In other words, the desired genetic trait need not be cytologically linked to the compound chromosome. We will now discuss the synthesis of compound chromosomes for different karyotypes, their behavior in experimental populations of *Drosophila melanogaster*, and their relevance to the genetic manipulation of natural populations of mosquitoes and other insect pests.

Synthesis of Compound Chromosomes

A compound chromosome is one in which two homologous arms are attached to the same centromere, as opposed to the structurally normal chromosome, in which nonhomologous arms are attached to a centromere (Fig. 1). In *D. melanogaster*, strains bearing compounds of either major autosome are genetically isolated from chromosomally normal strains, because all zygotes resulting from crosses of individuals having normal chromosomes with others having compound chromosomes carry lethal duplications and deficiencies of genetic material. On the other hand, a proportion of the zygotes produced by the mating of two strains having compound chromosomes will be genetically balanced and therefore viable.

The actual proportion of viable zygotes produced by a cross between two individuals bearing compound chromosomes of the type depicted in Fig. 1b depends on the segregational behavior of the compound chromosomes during meiosis. Although adequate cytological studies have not been done, the inheritance patterns of genetically marked compound chromosomes in *D. melanogaster* have provided a reasonably clear picture of their meiotic behavior (8-10). In females the left compound segregates from the right one at least 95 percent of the time, whereas in males assortment of the compounds is random or nearly so. Figure 2 shows that if the assortment of compounds in either or both sexes is random the expected zygotic viability is 25 percent, while if disjunction is entirely regular in both sexes the expected viability is 50 percent. Holm (9) reported that his

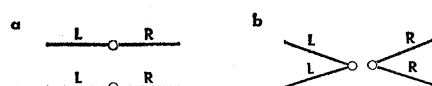


Fig. 1. A pair of homologous metacentric chromosomes, (a) with normal configuration, (b) compounded for both left and right arms.

strains with compound second-chromosomes had roughly 30 percent zygotic viability (egg hatch), and his strains with compound third-chromosomes 25 percent viability, in good agreement with the genetic expectation. From these and other observations on compound chromosomes (9, 10), and the known relationship between crossing-over and chromosome disjunction in *D. melanogaster* females (11), it is possible that the sex difference in the behavior of compound autosomes is related to the fact that in this species (as in most other higher Diptera), meiotic crossing-over is restricted to females. From this we may hazard a guess that in strains of other higher Diptera with compound autosomes, the zygotic viability will be in the region of 25 to 30 percent, whereas in species such as mosquitoes, in which crossing-over takes place in both sexes, the viability of compound strains may approach 50 percent. The proportion of viable zygotes produced by compound strains will be an important factor to consider in practical programs of pest control.

The original synthesis of compound autosomes in *D. melanogaster* has been described by Lewis (12) and his co-workers, and we suggest essentially similar procedures. For the initial step in the synthesis, special translocations must be developed and used as heterozygotes to generate gametes capable of capturing the newly induced compound arm. In the scheme outlined in Fig. 3, structurally normal females are irradiated and mated to males heterozygous for two reciprocal whole-arm translocations. A percentage of the male gametes will contain the genetic material necessary to balance (and therefore capture) new compound arms carried in the female gametes. The newly captured compound arm is identified by the inheritance of the appropriate maternal homozygous markers. It can be maintained temporarily by backcrossing to the double translocation heterozygotes. The complementary compound arm is made simply by mating irradiated normal females to males carrying the compound arm. The only survivors of such a cross will

either be nondisjunctants, or will contain the newly synthesized complementary compound arm. An important feature of this scheme is that, by using genetic markers on all four autosomal arms of the original irradiated females, any of four different compounded arms can be recovered, depending on the gamete used for recovery. Thus one genetic system can be used to establish strains carrying compounds of either of two different chromosomes. As suggested below, the availability of more than one such race of a pest species would be a significant asset for certain kinds of control programs.

The generation of compound chromosomes from acrocentric chromosomes, or from metacentric chromosomes with a dispensable heterochromatic arm, could be accomplished by a procedure such as that outlined in Fig. 4. In this case irradiation of the flies is necessary in only one step, because the initial individual that bears the compound chromosome need only be backcrossed to the strain with the translocation to make a true-breeding stock. The zygotic viability of a strain with this type of compound chromosome should be 50 percent.

Once an original strain with a compound chromosome has been synthesized, new strains with compound chromosomes can be made by routine procedures. One merely irradiates normal females of the desired genetic constitution, and mates them to males with compound chromosomes. The only surviving progeny should contain newly induced compound chromosomes and carry the introduced traits, or will have resulted from nondisjunction.

When the desired gene is linked to a chromosome not homologous to the compound one, the procedure outlined in Fig. 5 might be followed. This feature of compound autosomes gives a significant advantage over multiple translocations or cytoplasmic incompatibility for pest control purposes, because it enables transfer of any genetic trait in a single step from a structurally wild-type strain into the genetic background of the strain with the compound chromosomes.

Since genetic techniques offer the only practical means of collecting translocations, some knowledge of the genetics of a pest will be a prerequisite to the synthesis of compound chromosomes. Species with a small number of easily distinguishable chromosomes offer special advantages, since structural changes detected genetically can be

readily confirmed cytologically. For these reasons certain dipteran pests should prove to be the most susceptible to this kind of approach. In fact, the genetics of some dipterans [for example, *Musca domestica* (13), *Lucilia cuprina* (14), *Aedes aegypti* (15), *Culex tritaeniorhynchus* (16), and possibly *C. fatigans* (17)] are already sufficiently well known to make the synthesis of compound chromosomes feasible. Orthopterans, because of the large size of their chromosomes, are another possible group, as are some species of Coleoptera and Blattodea. It is difficult to assess the prospects for Lepidoptera and Hemiptera in which the chromosomes are holocentric, without more information on the meiotic behavior of this type of chromosome.

Population Genetics of Compound Chromosomes

When two strains, one with normal chromosomes (AA) and the other with a pair of its autosomes compounded (CC), are mixed and allowed to mate, three karyotypes will result, AA, CC, and the hybrid AC. The subsequent behavior of a population derived in this way conforms to the special case of negative heterosis where the heterozygote (AC) has zero fitness. It can be shown easily that the equilibrium, $\hat{p}$, of the CC type, is given by $\hat{p} = 1/(1 + W)$ where W is the Darwinian fitness of the CC type relative to the AA type. Furthermore, this equilibrium is unstable. In the case of compound chromosomes the intuitive explanation for the unstable point is straightforward: when either type, CC or AA, is extremely rare it will become even rarer because most of its mating partners will be the common type with which it is sterile, while at the same time the common type will enjoy mostly fertile matings with its own kind. By arguing in continuity, it follows that there must be some intermediate mixture above which one type will win and below which it will lose. The location of this unstable equilibrium depends on the relative fitness of the two types, W . Thus, from zygotic viability alone, CC, in contrast to AA, should give $W = 0.25$ and an unstable point, $\hat{p} = 0.80$. That is, the frequency of the strain with the compound chromosome must exceed 80 percent in order for the compound chromosome to spread autonomously and become fixed. Similarly, if two strains each with a different com-

pound chromosome are placed together they should be equally inviable, giving $W = 1$ and an unstable point of $\hat{p} = 0.50$.

While negative heterosis and the resultant unstable equilibrium is an elementary feature of population genetic theory, it has not been demonstrated and studied experimentally. This omission probably stems from the lack of genetic systems which behave in this way and the belief that, in any case, such a system is not an important evolutionary process. [However, White (18) would argue otherwise.]

Using *D. melanogaster*, we constructed two sets of experimental populations: one in which two different compound chromosomes were placed in competition, and another, more directly related to pest control problems, in which a strain with a compound chromosome competed with a chromosomally normal strain. One of the strains with compound chromosomes had chromosome II compounded and carried several markers, one of which was *dumpy*; this will be designated C(2):*dp* hereafter. The other strain had chromosome III compounded and carried, among other identifications, the marker *radius incompletus*; this will be designated C(3):*ri*. All populations were carried in half-pint culture bottles in discrete generations. In the first experiments, with the two compound chromosomes, we used 11 populations, all founded in the same way, as fol-

lows: ten inseminated females from each of the C(2):*dp* and C(3):*ri* strains were allowed to lay eggs together. The small number of founders was used to ensure a spread of initial frequencies around 0.5. Their offspring were regarded as generation zero, and each subsequent generation was established by collecting eggs over a 24- to 48-hour period from the flies comprising the previous generation. Population sizes fluctuated between 100 and 400 individuals. More details of the experimental procedure together with a statistical analysis and some extensions of the theory will appear elsewhere.

The results of this first experiment are summarized in Fig. 6, where the frequency of C(2):*dp* is given as a function of generation number. It is quite evident that this system is, indeed, governed by an unstable equilibrium in the vicinity of 50 percent, as predicted. The final outcome is strongly influenced by initial frequencies, and presumably would be completely so, were it not for early stochastic effects in these finite populations. The changes are very rapid, with one or the other compound chromosome becoming fixed in a mean time of 5.3 generations. In fact, this system, once under way, moves faster than a system in which there is a recessive lethal gene since almost all matings of the rare homozygous form produce heterozygotes which have zero fitness.

In the second experiment C(2):*dp* was placed in competition with a chro-

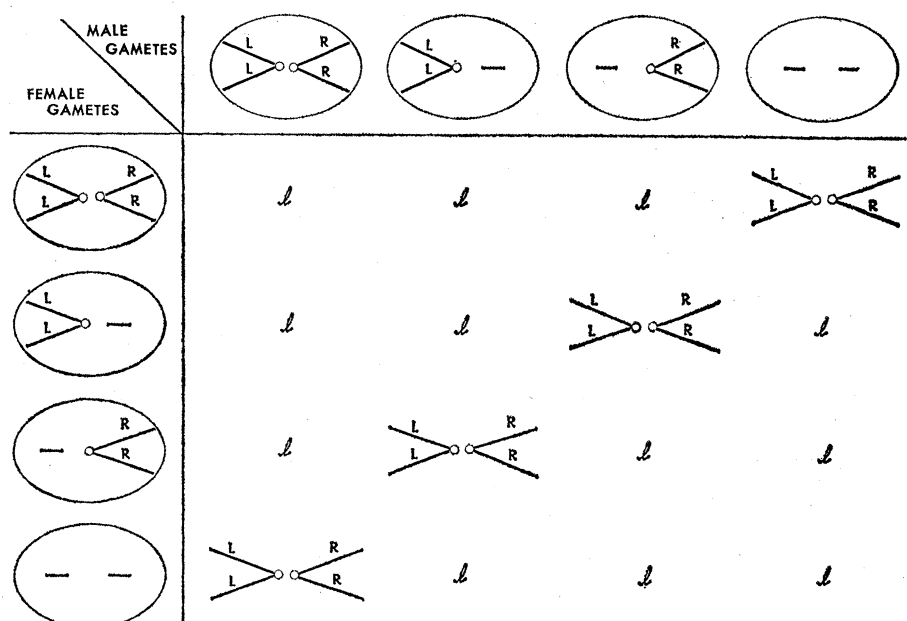


Fig. 2. Matrix of zygotic types from cross between two individuals carrying compounded left and right arms for the same chromosome. If segregation is random, 16 zygotes are formed of which 12 are unbalanced and lethal while 4 carry the parental arrangements and are viable.

mosomally normal strain. As already noted, because of the low fertility of the $C(2):dp$ strain we expect the unstable point to be displaced to the vicinity of $\bar{p}=0.80$. Thirteen populations were initiated with small numbers of normal females placed together with larger numbers of $C(2):dp$ females, such that the starting frequencies of $C(2):dp$ ranged from 71 to 96 percent. Figure 7 summarizes the outcome of these experiments.

Once again it is evident that there is an unstable point. This system moves even faster, the frequency of one or the other strain becoming fixed in a mean time of 2.4 generations. However, the unstable point is in the vicinity of 0.90 rather than 0.80 as predicted, and so we estimate that the fitness of $C(2):dp$ is 0.10 rather than 0.25 of the fitness of the chromosomally normal strain. This could easily result from the markers in $C(2):dp$ stock or, perhaps, from the intrinsic effects of the chromosome rearrangements which manifest themselves after egg hatch. Newly synthesized compound chromosomes could, presumably, be screened for higher fitness approaching the maximum of 0.25. In two other experiments (19) results similar to those in Fig. 7 were obtained with unstable points of about 0.85.

Discussion

We have shown that for some insect pests it might be possible to synthesize what amounts to an artificial species which, with relation to the field population, displays complete reproductive isolation operating in the postmating phase, but is not behaviorally isolated in the premating phase. These two conditions suffice to create an unstable equilibrium and thus the transporting mechanism, while the postmating isolation permits the transport of any sort of complex genotype located in any part of the genome. We will show in a later publication that a certain amount of behavioral isolation merely affects the location of the unstable point, destroying it only when such isolation is complete.

The synthesis of a compound chromosome rearrangement demands considerable effort but its worth is dependent on how strains of this nature could be employed in a pest management program. To cite a single example: *C. fatigans* is the major vector for periodic Wuchererian filariasis in Asia, and this disease in India alone claims some 8 million advanced cases at any one time, 12 million with earlier stages of the disease and a further 120 million in danger of infection (20). Mattingly

(21) estimates a world figure of over 200 million cases of filariasis at any one time and suspects that this figure is increasing. *Culex fatigans* is resistant to most insecticides (21) and deteriorating sanitation is favoring its spread in both Africa and Asia. It is also refractory to classical biological control, and the sterile male technique might require the release of prohibitively high ratios of sterile males where population size is significantly regulated by density-dependent larval competition. Should the ratio of sterile males released be too low, the introduction of zygotic mortality through matings of field females with sterile males may be offset by a corresponding reduction in larval mortality through a lowering of competition for limited nutrients, without any effect on the subsequent size of the adult population (22). Transporting mechanisms such as compound chromosomes should be insensitive to density-dependent regulation.

A satisfactory solution for *C. fatigans* might be the displacement of the resident population over large areas, where the mosquito's nuisance value is high, by a strain that has compound chromosomes and also possesses one or more genetic mechanisms to prevent development of the filarial parasite in the mosquito. It may be preferable to dissemi-

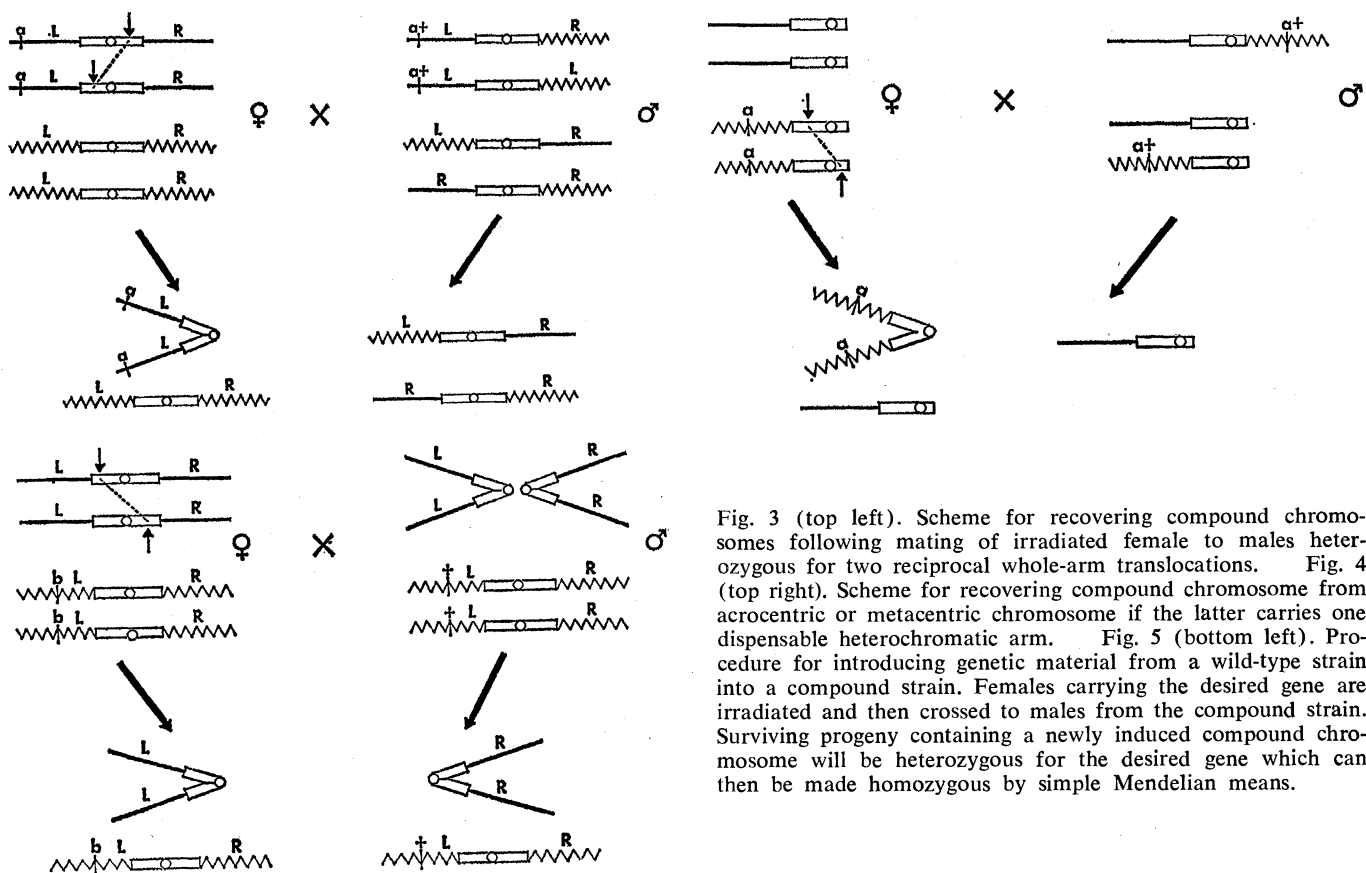


Fig. 3 (top left). Scheme for recovering compound chromosomes following mating of irradiated female to males heterozygous for two reciprocal whole-arm translocations. Fig. 4 (top right). Scheme for recovering compound chromosome from acrocentric or metacentric chromosome if the latter carries one dispensable heterochromatic arm. Fig. 5 (bottom left). Procedure for introducing genetic material from a wild-type strain into a compound strain. Females carrying the desired gene are irradiated and then crossed to males from the compound strain. Surviving progeny containing a newly induced compound chromosome will be heterozygous for the desired gene which can then be made homozygous by simple Mendelian means.

nate a strain with a conditional lethal gene, such as one susceptible to low temperatures, but it is not clear whether a vacated niche provides a preferable long-term solution. Indeed, the mere presence of a refractory strain with compound chromosomes retards and may prevent reentry of the strain that permits development of the parasite. In this instance the permanence of the population displacement will be determined by events along the boundaries of the areas occupied by the strain with compound chromosomes and the wild-type strain (23). Stability in boundary regions could be reinforced by further releases of the refractory strain with compound chromosomes.

Examples of highly stable distribution patterns of chromosome races exist both for insects (24) and mammals (25). While such examples are not uncommon we must suppose that displacements in natural populations overcome enormous odds. Limitations are not imposed by the frequency of suitable chromosomal rearrangements arising but rather by the necessity for these rearrangements to exceed a frequency in the population below which they would incur considerable disadvantage. The importance of population structure has been inferred as the critical factor in this process (24); because of larger populations and higher mobility of in-

dividuals, species such as mosquitoes are less inclined to display the amount of chromosomal diversity seen in wingless grasshoppers where both population size and vagility are low. By our selecting suitable genetic rearrangements (for example, compound chromosomes) and releasing individuals with these rearrangements in excess of the unstable point it would appear that we would meet those conditions necessary for population displacement that otherwise would be rarely satisfied, say, for mosquito species. We therefore suggest that what we are proposing constitutes a field experiment which simulates what may be a not unimportant natural evolutionary event.

If we assume that the fertility of the strain with compound chromosomes lies between 0.25 and 0.5, it follows that we have to release in excess of four insects for every insect in the field. We could perhaps provide the released insect with a temporary advantage by including, in its genotype, genes for insecticide resistance which are absent or rare in the released area (7). In this manner the fitness of the compound strain could exceed that of the native strain and considerably fewer insects would have to be released. Application of the insecticide could cease when the released strain exceeded the normal equilibrium frequency.

So far we have assumed complete genetic isolation between a strain with compound chromosomes and the wild-type strain. A breakdown in this isolation could occur if the compound strains were to produce a wild-type gamete which combined with a similar wild-type gamete or, conversely, if the wild-type strain were to give rise to a gamete with a compound arm *de novo*. Both events have finite probabilities and consequently, given large enough populations and ample time, such events would occur. Clearly such events would not alter the direction of general displacement, but would result in a transfer of genetic material between the two strains. Such a transfer of material from the compound strain would not matter because (i) the wild-type strain is being displaced, and (ii) the material transferred is acceptable (that is, it determines such factors as vector refractoriness). The consequences of the converse are more difficult to evaluate. Firstly, we do not know how frequently a wild-type strain produces spontaneously a gamete with a complementary compound arm. The occurrence of such a gamete would permit the transfer of genetic material albeit in low frequency. Its effect could be disastrous if our control plan included displacement of insecticide resistance with susceptibility. Where displacement of a vector form is

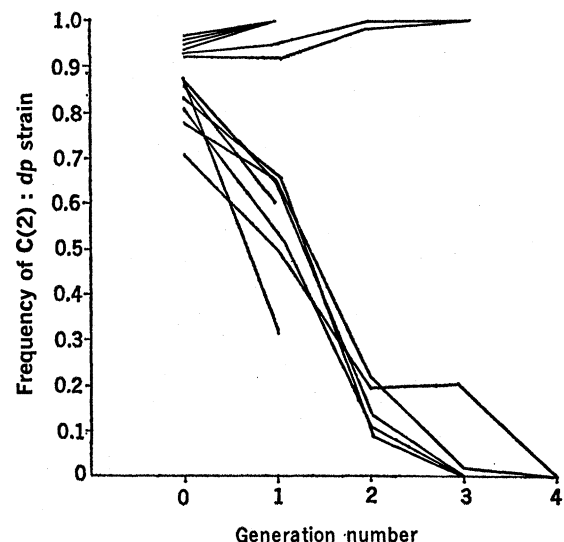
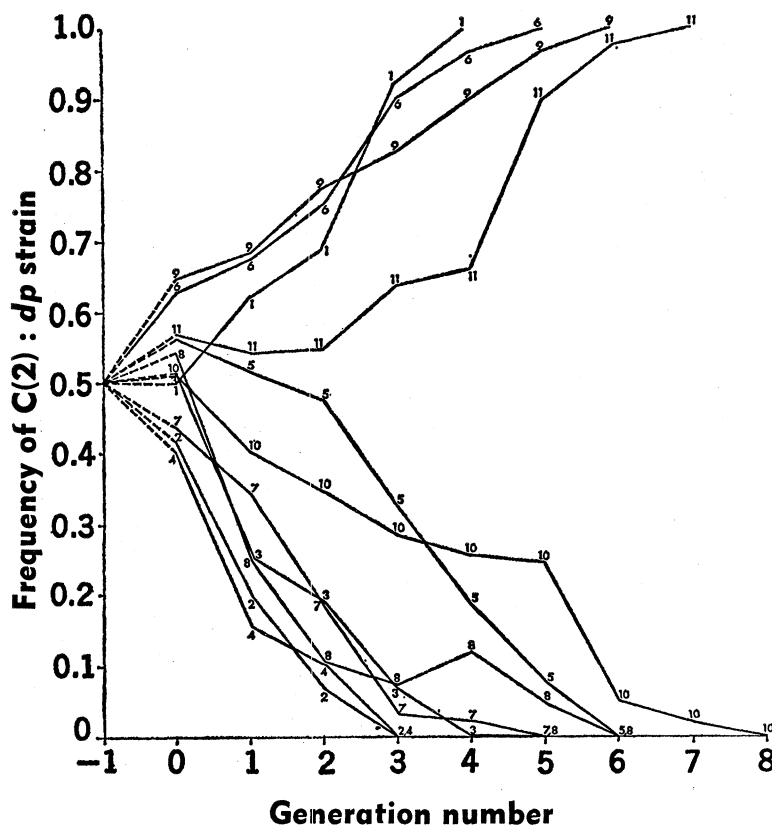


Fig. 6 (left). Change in frequency of C(2) : dp strain in competition with C(3) : *ri* strain. The unstable point is about 0.5. Fig. 7 (right). Change in frequency of C(2) : dp strain in competition with structurally wild-type strain. The unstable point is about 0.9.

intended, the damage would depend on the intrinsic selective advantage to the vector of susceptibility to the parasite. If we assume that susceptibility to the parasite conveys little advantage, then the frequency of such susceptibility may remain sufficiently rare for a sufficient length of time for disease transmission to be interrupted. Another avenue for leakage would be fusion of a gamete from the strain with compound chromosomes, in which both the left and the right arms of the chromosome are compounded, with a gamete from the wild-type strain in which nondisjunction at meiosis led to the exclusion of both wild-type homologs of the compound chromosome or the complete converse. Thus it might prove necessary to displace the liberated compound strain by another strain compounded for a different autosome. The unstable point throughout the second displacement would be about 0.5 because the strains involved would have roughly equal fitness. Leakage during the second displacement would require the simultaneous occurrence of two rare events to produce a viable hybrid. This hybrid, compounded for both autosomes, would in turn have to rely on several rare events to produce viable offspring.

Another area of uncertainty relates to the adaptability of the parasite when confronted with a refractory insect population. Its response is unpredictable, particularly for diseases such as filariasis, which may leave diseased people infectious for some years. If it is impracticable to exterminate a species of mosquito entirely from an area, we may have to copy the system used by plant breeders in their struggle to stay one step ahead of rust, and continually isolate new refractory genotypes.

Our intention has not been to suggest, in any detail, suitable control measures for any particular insect pest, but rather to outline a technique for effecting gene substitutions in natural populations of insects, where such changes would be of some benefit to man. Few insect groups appear suited to the detailed manipulations required before the synthesis of strains with compound chromosomes is possible. We have outlined some of these requirements, and think they can be met for some dipteran pests such as mosquitoes, blackflies, houseflies, blowflies,

fruit flies, and possibly others in other orders of insects. It is possible that there are properties of natural populations of which we are unaware and which could nullify the suggestions made here. However, large-scale releases of the type described could be regarded as perturbation experiments, which, although not serving their original purpose, could supply important ecological information. Strains of *D. melanogaster* with suitable compound chromosomes already exist and consideration might be given to field studies particularly in areas where the fly is a minor pest. These attempts could delineate problems and possible solutions while compound chromosomes in strains of insect species that are more important to man are being prepared.

Summary

Current theory on the control of insect pests by genetic manipulation is reviewed. An outline is given of the synthesis and behavior of a particular type of chromosome rearrangement, called a compound chromosome, for altering the genetic composition of natural populations of a particular pest. In effect, the process aims to displace field populations of the pest through the release of a new form where pre-mating isolation behavior is absent but postmating isolation, through genetic death of the hybrid, is complete. This new form would either carry a conditional lethal genotype or remove the noxious features of the pest, such as vector capacity. Displacement of the old form follows from the instability generated by the hybrid lethality and could take as little as five generations for completion. It is claimed that pest control by genetic displacement parallels a common evolutionary process. The list of pests susceptible to this form of control is limited, but includes several important pest species such as mosquitoes and other dipterans.

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