Why is Mendelian Segregation so Exact?

James F. Crow

“Clearly a higher plant species is at the mercy of its pollen grains. A gene which greatly accelerates pollen tube growth will spread through a species even if it causes moderately disadvantageous changes in the adult plant.” J. B. S. Haldane, 1932

Summary

The precise 1:1 segregation of Mendelian heredity is ordinarily taken for granted, yet there are numerous examples of ‘cheating’ genes that perpetuate themselves in the population by biasing the Mendelian process in their favor. One example is the Segregation Distortion system of Drosophila melanogaster, in which the distorting gene causes its homologous chromosome to produce a nonfunctional sperm. This system depends on three closely linked components, whose molecular basis is beginning to be understood.

The system is characterized by numerous modifiers changing the degree of distortion. Mathematical theory shows that unlinked modifiers that change the degree of distortion in the direction of Mendelian always increase in the population. This provides a mechanism for removing cheaters and preserving the honesty of the Mendelian gene-shuffle.

Introduction

Geneticists take Mendel’s first law as dogma, usually not questioning whether it might be otherwise. The rule says that each of a pair of alleles has an equal chance of being transmitted to the next generation. The explanation seems obvious – the regular segregation of homologous genes in meiosis.

Yet there are several examples of genes and chromosomes that violate these laws, that cheat by one way or another getting themselves transmitted to more than 50 percent of the progeny. Such genes are unusual, but they are by no means unknown. They are widely scattered through the animal and plant kingdom, but are of low frequency in any particular population. Since they enjoy a large transmissional advantage, why do they remain rare?

It is obvious that cheating genes are harmful to the population, for in addition to possible harmful pleiotropic effects, they decrease the fairness of the gene-testing process of Mendelism and natural selection. But this is a group selection argument, which evolutionists prefer to avoid. Is there an individual selection mechanism favoring Mendelism? The answer is yes, as I shall show later.

One way in which a gene can cheat is by somehow enhancing the success of the gamete carrying it. As Haldane noted long ago (see the quotation at the beginning of this article), a gene that gives its pollen a competitive advantage will spread through the population even if it harms the plant. Animals seem to have avoided this problem by turning off most gene activity during sperm maturation. But a more subtle form of cheating occurs when the segregation bias is a consequence of the meiotic process.

The term ‘meiotic drive’ was coined by Sandler and Novitski. They envisaged systems in which, as a result of something associated with meiosis, one of the meiotic products is preferentially transmitted. They cited two examples, one from Drosophila and one from maize, in which a chromosome is preferentially included in the egg nucleus rather than a polar body. They also noted two examples in which male transmission ratio is distorted, ‘sex-ratio’ in Drosophila pseudoobscura and the t-locus in mice. The word has been extended to apply to preferential transmission when the meiotic mechanism is not clear (indeed, Sandler and Novitski were not sure about the mouse example). I shall term a chromosome, haplotype, or gene that is favored by such a process as ‘driven’ and the departure from normal Mendelian ratios as ‘segregation distortion’.

This article is divided into two parts. In the first, I describe the Segregation Distortor system in Drosophila melanogaster as a well studied example of meiotic drive. In the second part, I consider the population consequences, in particular the effect of modifiers that change the degree of distortion.

Segregation Distortion in Drosophila

In 1956, Yuichiro Hiraiizumi, then a graduate student at the University of Wisconsin, was studying the effects on viability of a number of heterozygous chromosomes that were lethal when homozygous. These chromosomes had been extracted from flies collected in a natural population. Among several hundred chromosomes were six that were transmitted in grossly disproportionate ratios, to essentially 100 percent of the progeny rather than the canonical 50 percent.

The driven chromosomes had no overt phenotype. The only clue to their presence was the differential transmission of linked marker genes. Hiraiizumi quickly established that the distortion occurred only in heterozygous males; heterozygous females produced normal Mendelian ratios. Other possibilities, such as postzygotic deaths, were ruled out.

In the spring of 1957, Larry Sandler was awarded a postdoctoral fellowship to work in my lab. His article
with Novitski(1) appeared about the same time and I was delighted to tell him of Hiraizumi’s having found a beautiful example of the very thing that he had written about. Its occurrence in the well studied Drosophila melanogaster promised ease and depth of genetic analysis. Sandler and Hiraizumi joined forces and the early findings in this system are due to their happy partnership(5).

The SD (for segregation distortion) region mapped close to the centromere of Chromosome 2. Hiraizumi’s original six chromosomes were of two types. Five were lethal when homozygous, the sixth was not. All had inversions in the right arm or the centromeric region of the second chromosome, but the inversions in the two types were different. The lethality turned out to be associated with an inversion rather than with SD itself. The system has been reviewed several times(6-7).

Over the next few years, SD was found throughout the world. Almost every population that was extensively sampled had SD chromosomes, but always in low frequency, less than 5 percent. With a very small number of exceptions, every SD chromosome had one or more inversions in the right arm of Chromosome 2 or around the centromere. The explanation was soon obvious. There are genes near the centromere and in the right arm of 2 that enhance the degree of distortion. It is clearly advantageous to the drive system for such enhancing genes to be linked to the driven locus, and the inversions serve this purpose by reducing recombination. The inversions in different SD strains from around the world differ. Often they are whatever inversion is common in the region, as if the SD chromosomes had spread through the world, picking up useful inversions as they went. It is clear that no particular inversion is required, but that having one or another combination of inversions is important. Some examples of the kinds of inversions found in various populations are shown in Fig. 1.

A series of cytogenetic experiments have established that the system has three main components(8), along with a host of modifiers. The three are: Sd, the most important distorter; E(SD) (Enhancer), originally thought to be only an enhancer of Sd, but recently shown to have distorting activity independent of Sd(9); and Rsp (Responder). Responder exists in two principal states, Rsp+ and Rsp− for sensitive and insensitive to the effects of Sd and E(SD). The chromosome locations of these three loci are shown in Fig. 1.

Fig. 1. Examples of inversions found around the centromere and in the right arm of Chromosome 2 in various SD strains. The symbols at the right are arbitrary designations of different strains.

![Fig. 2. The location of the three major components of the Segregation Distorter system on Chromosome 2. The hatched area is centromeric heterochromatin, and the centromere is indicated by a circle. The components are Segregation Distorter (Sd), Enhancer (E(SD)), and Responder (Rsp).](image)

Fig. 2. Since E(SD) has effects similar to those of Sd, I shall not discuss it further.

Throughout this article I shall follow established convention and use SD to designate the driven chromosome with all its components, while reserving Sd for one specific component.

The distortion phenotypes of various chromosome combinations are as follows:

<table>
<thead>
<tr>
<th>Male genotype</th>
<th>Chromosome transmitted in excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sd Rsp+/Sd+ Rsp+</td>
<td>Sd Rsp+</td>
</tr>
<tr>
<td>2. Sd Rsp+/Sd− Rsp+</td>
<td>Sd+ Rsp+</td>
</tr>
<tr>
<td>3. Sd Rsp+/Sd+ Rsp+</td>
<td>Neither</td>
</tr>
</tbody>
</table>

When Sd is present a sperm receiving Rsp+ is dysfunctional. The distorting SD chromosome in natural populations is Sd Rsp+. The wild-type chromosome, sensitive to SD effect is Sd+ Rsp+. Insensitive, Sd+ Rsp− chromosomes also exist in natural populations, often at quite high frequencies, which helps explain the low frequency of SD. The second SD type, Sd Rsp− is a suicide chromosome, not found in natural populations because of near-zero transmission, but it can be constructed in the laboratory from rare recombinants.

The components of the system function irrespective of their chromosomal location, but Sd is most effectively maintained in the population if Rsp+ is on the homolog, and enhancers are linked to Sd. The inversions around the centromere and in the right arm of Chromosome 2 keep the system intact by preventing the components of the system and their linked enhancers from being randomized by recombination.

Components of the system can be moved around by translocation without noticeable effect. The most interesting of these are translocations to the X and Y chromosomes, with predictable effects on the sex ratio. Lyttle(10) produced a 2;Y translocation that yielded almost entirely males; most experimental populations soon became extinct for want of females. Some were saved from extinction by acquiring modifiers that reduced the degree of distortion. One of Lyttle’s populations managed to escape extinction by accumulating extra Y chromosomes(11). The XXY females produced enough nondisjunctional XX gametes to ensure a few females each generation and thus kept the population from extinction. Nature is indeed a clever opportunist.
Many years ago it occurred to me that one situation in which meiotic drive would be distinctly advantageous would be in a balanced lethal system. If there were meiotic drive in both sexes, but in opposite directions, then the 50 percent mortality could be reduced to zero. My attempt to select for female drive opposite in direction to that of male drive in population cages where $SD$ was incorporated into a balanced lethal system failed. But when I discussed this with A. H. Sturtevant, he told me that nature had already anticipated me and that such a system operates in the ever-surprising evening primrose. Renner(12) found that in the balanced lethal system formed from complex translocations in Oenothera muricata the functional pollen is of one chromosome type whereas the successful egg nucleus is of the opposite type. Charlesworth(13) has discussed how the Oenothera system could evolve.

Early experiments(14,15) showed that the mechanism of distortion is failure of non-$SD$ sperm cells to mature properly. The abnormalities are easily visible by electron microscopy; the abnormal sperm nuclei do not condense normally and the spermatoozoon do not individualize in the syncytium(16). What causes the abnormality is not known, although there is a failure of lysine-arginine transition in the spermatid histones(17). Although the abnormality appears in the spermatozoon, the interaction between $Sd$ and $Rsp^\prime$ must have occurred earlier while the two elements were in the same nucleus. This is supported by finding that the temperature-sensitive period for the degree of distortion is during meiosis(18). Somehow the $Sd$ must communicate with $Rsp^\prime$, ordering it to self-destruct. This is all the more remarkable because it is known that a Drosophila sperm can function with no chromosomes at all(19). Therefore the sperm dysfunction is a positive act of sabotage, not simply the failure to carry out some normal sperm-maturation process. This is undoubtedly one reason why such systems are as rare as they are.

Both $Sd$ and $Rsp^\prime$ have positive functions; they are nemorphs in Muller's convenient notation. This is another reason for the rarity of such systems. The strongest evidence comes from deletions. A deletion of $Sd$ leads to normal 1:1 segregation. Likewise, deletions of $Rsp$ are insensitive(8,20). A system such as this seems extremely unlikely, a priori, since not only must there be two components, but the two must be on homologous chromosomes. They must also be closely linked to keep the system from breaking down. Possibly the absence of recombination between X and Y accounts for what appears, at least superficially, to be a more common occurrence of sex-ratio drive systems than would be expected from the small fraction of genetic material that is in the sex chromosomes. I should note, however, that distorted sex ratios are easily observed, whereas autosomal drive systems are detected only if appropriately placed markers happen to be present.

Molecular analysis has revealed a great deal of structural detail, but alas has thus far brought no insight into the mechanisms. The responder region turns out to be a repeated sequence of 120 bp AT-rich units. The degree of sensitivity is strongly correlated with the number of repeats. Insensitive responders have a dozen or so units, while the most sensitive — so-called supersensitives — have thousands.(7,21) Structural features are similar to satellite DNAs and suggest protein binding possibilities(22).

Powers(7,23) has found that the $Sd$ locus is complex. All $Sd$ chromosomes have a 12Kb EcoRI restriction fragment whereas the corresponding fragment in normal, $Sd^+$ chromosomes is 7Kb. Further analysis showed that indeed there is a 5Kb direct duplication. This immediately negates one hypothesis, that $Sd$ had an extra-Drosophila origin(6). Furthermore, the $Sd$ region, but not the duplication, has been found in related species(23).

Detailed analysis has revealed that the duplication encodes a 4Kb transcript. There are seven cDNA classes involving at least four open reading frames. These have the potential for encoding four different polypeptides. In all of them, the same 3' open reading frame is used; they differ by the exons that are spliced at the 5' end. The entire region has not yet been sequenced, in particular the junction between the two duplications. It is known, however, that simply duplicating the 7Kb region elsewhere in the genome does not produce distortion. Furthermore, introducing the $Sd$ duplication by germline transformation does not produce distortion. This is not as surprising as it may at first seem because Powers(23) has shown that some of the cDNAs are derived from genomic DNA that extends beyond the duplicated region, suggesting that other regions are needed for the effect.

So, although molecular analysis has revealed a great deal of detail it has thrown little light on the interesting mechanistic problems: How does $Sd$ instruct $Rsp^\prime$ to sabotage its sperm, and how does $Rsp^\prime$ do it? One might suspect that $Sd$ produces a protein product that interacts with the $Rsp$ locus, and indeed this may be the case. Direct evidence is missing, however; proteins encoded by the duplication do not bind to cloned $Rsp$ DNA(23), although these negative results have a variety of explanations.

The cloning of $Rsp$ has filled a troublesome gap in our understanding of the population dynamics of the system. Charlesworth and Hartl(24) showed that with realistic values of the distortion and fitness parameters, the system equilibrates with a low frequency of $SD$ chromosomes, and with both sensitive and insensitive responders present in the population. This is what is observed in nature. It is obvious that when most responders are sensitive, $SD$ will rapidly increase. When $SD$ becomes common there is strong selection for insensitive responders to replace sensitive ones. But then, why don't sensitive responders disappear? An obvious answer is that, other than in their interaction with $SD$, they are selectively favored.
For many years it was impractical to test this hypothesis, for Rsp\(^{r}\) and Rsp\(^{l}\) could be distinguished only by prohibitively labor-intensive progeny tests. Wu’s demonstration that Rsp is a repeat unit means that the Rsp genotype can be distinguished in a single fly. He demonstrated clearly that in the absence of SD the sensitive responders are selectively favored\(^{25}\), thus providing the missing datum required to make the Charlesworth-Hartl theory complete and at the same time providing evidence for a fitness function of satellite DNA.

A recurring feature in SD research has been the finding of modifier loci. These are scattered over the genome, and a number have been found, despite there being no systematic search. It is the consequence of such modifiers to which I now turn.

### Meiotic Drive in Populations

Consider what happens to a meiotic drive system, such as SD or the very similar l-locus in mice, when mutations arise that modify the degree of distortion. I shall give an elementary version of some sophisticated mathematical analyses by a number of people\(^{24,26-35}\). Feldman\(^{36}\) has written a recent, concise comparison of meiotic drive systems with Mendelism.

The distorting allele will be designated by D and the sensitive alternative on the homologous chromosome by S. (I shall treat D and S as alleles, although as we have just seen in the SD system, they are likely to be closely linked loci in homologous chromosomes.) From a D/S heterozygote the proportion of D gametes is k.

To simplify the analysis, assume equal meiotic drive in both sexes. This is biologically unrealistic, for most drive systems involve one sex only. But if the proportion of D gametes is different in the two sexes, a unisex k that is the arithmetic mean of the two values leads to essentially the same population properties. This artifice obviates a great deal of tedious algebra and makes it easier to understand the analysis\(^{26,37}\).

I’ll assume the standard population model that fertility in the two sexes is multiplicative and mating is random. The model can be set forth as

<table>
<thead>
<tr>
<th>Genotype</th>
<th>D/D</th>
<th>D/S</th>
<th>S/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>(w_1)</td>
<td>(w_2)</td>
<td>(w_3)</td>
</tr>
<tr>
<td>Zygotic frequency</td>
<td>(p^2)</td>
<td>(2pq)</td>
<td>(q^2)</td>
</tr>
</tbody>
</table>

in which \(p+q=1\). Recalling that D/S heterozygotes produce D and S gametes in the ratio k/(1−k), we can write the frequency of the D allele in the next generation as\(^{28}\)

\[
p' = \frac{p^2w_1 + 2pqw_2k}{\bar{w}}
\]

(1)

\[
\bar{w} = p^2w_1 + 2pqw_2 + q^2w_3
\]

(2)

Equating p to \(p'\) yields the equilibrium value

\[
p = \frac{w_3 - 2kw_2}{w_1 - w_2 + w_3}
\]

(3)

giving a stable polymorphic equilibrium if \(2kw_2 > w_1\) and

\(2(1-k)w_2 > w_3\). When \(k=1/2\), \(w_2 > w_1, w_3\) provides the standard condition for a stable overdominant equilibrium.

A driven locus that is unopposed by selection will quickly sweep through a population. After it is fixed, there is no longer any distortion and the population behaves the same as before the mutant arose. How often such things happen is anybody’s guess. They might be detected by distorted ratios in hybrids between a population in which this had happened and another population in which it had not. Searches for such behavior in interspecific hybrids have so far not revealed anything\(^{37}\).

Fig. 3 shows a situation in which the drive \((k=0.8)\) is sufficient to overcome a selective disadvantage. In this case the driven gene goes to fixation, leaving the population with a fitness of 0.7 relative to the pristine value. A driven gene (or one linked to it) can thus sweep through the population, causing a lowering of population fitness and conceivably causing its extinction while leaving no clue as to the cause.

Fig. 4 shows the dynamics of a driven allele that is lethal when homozygous and slightly deleterious when heterozygous. With \(k=0.7\) the allele frequency equilibrates at 0.41 and the population fitness is reduced by about 15 percent. Known cases of meiotic drive are, of course, of this sort – those in which the driven locus remains segregating. I shall now discuss the effect of a gene that modifies the k value in such a case.

### Effect of a Modifier

Assume that the D,S system is in polymorphic equilibrium as in the last example. Now consider a second locus that has no effect except to modify the value of \(k\) at the D,S locus. A modifier allele that makes the \(k\) value higher will be designated as \(H\), one making it lower by \(L\). The segregation at the modifier locus is,
of course, normally Mendelian. The modifier allele is assumed to start at a low frequency.

**Modifer genotype**  
- \( H/H \)  
- \( H/L \)  
- \( L/L \)  

**k at the D,S locus**  
- \( k_1 \)  
- \( k_2 \)  
- \( k_3 \)  

**Gamete**  
- \( DH \)  
- \( DL \)  
- \( SH \)  
- \( SL \)  

**Zygotic frequency**  
- \( x_1 \)  
- \( x_2 \)  
- \( x_3 \)  
- \( x_4 \)  

Let \( r \) be the proportion of recombinants between the two loci, and to simplify the equations, let \( z_1 = 2k_1 \) and \( y_1 = 2(1-k_3) \). We can then write the recurrence equations as:

\[
\begin{align*}
    x_1 &= \left[ x_1^2 w_1 + x_1 x_2 w_1 + x_1 x_3 w_2 z_1 + x_1 x_4 w_2 z_2 - z_2 D \right] / \tilde{w} \\
    x_2 &= \left[ x_1 x_2 w_1 + x_2 w_1 + x_3 x_4 w_2 z_3 + x_2 x_4 w_2 z_3 + z_2 D \right] / \tilde{w} \\
    x_3 &= \left[ x_1 x_3 w_2 y_1 + x_2 x_3 w_2 y_1 + x_3^2 w_3 + x_3 x_4 w_3 + y_2 D \right] / \tilde{w} \\
    x_4 &= \left[ x_1 x_4 w_2 y_1 + x_2 x_4 w_2 y_2 + x_3 x_4 w_3 + x_4^2 w_3 - y_2 D \right] / \tilde{w} \\
    D &= rw_2(x_1 x_4 - x_2 x_3) \\
    p &= x_1 + x_2, \quad q = x_3 + x_4.
\end{align*}
\]

The equation for \( \tilde{w} \) is still given by Equation 2, since only the D,S locus has fitness effects.

**Some Numerical Results**

Equations 4 are easy to write, but the mathematical analysis is still incomplete. (Surprisingly, a complete analysis of two loci has not yet been made, even without distortion.) Yet some important biological conclusions are easy to see. I will use a numerical example to illustrate a situation that seems both typical and biologically interesting.

Assume that the D,S locus has reached an equilibrium with \( p = \bar{p} \). Similar to Fig. 4, \( k_0 = 0.7 \), \( w_1 = 0.1 \), \( w_2 = 0.95 \), and \( w_3 = 1.0 \). Substituting these into Equation 3 gives \( \bar{p} = 0.4125 \) and \( \bar{q} = 0.5875 \). We now consider two cases, (a) a newly arisen modifier that increases the degree of distortion and (b) one that decreases it. In each case the heterozygous modifier produces distortion at the D,S locus equal to the mean of the two homozygotes. The parameters are:

- (a) Increasing distortion: \( k_1 = 0.9 \), \( k_2 = 0.8 \), \( k_3 = 0.7 \).
- (b) Decreasing distortion: \( k_1 = 0.7 \), \( k_2 = 0.6 \), \( k_3 = 0.5 \).

In each case, the mutation changing the \( k \) value starts at a low frequency, but at approximate gametic equilibrium. Some representative numbers are given in Table 1. The upper part of the table gives an example of case (a) and the lower one of case (b). The last three columns give the mean fitness, \( \bar{w} \), the mean \( k \) value of D,S heterozygotes, \( \bar{k} \), and the mean segregation ratio in the population, \( \bar{k} \), including those genotypes in which \( k = 1/2 \).

- (a) **Modifier increasing distortion.** When \( r \) is small, a \( k \)-enhancing modifier, \( H_i \), becomes associated with the \( D \) gene. At equilibrium the two common chromosomes are \( DH \) and \( SL \) and \( k = 0.8 \). The population fitness is reduced to a fraction, 0.597, of what it would be without the drive system. With increasing \( r \), the enhancing modifier increases only slightly and for large \( r \) doesn't invade the population at all.

- (b) **Modifier decreasing distortion.** When \( r \) is small, a \( k \)-depressing modifier, \( L_i \), becomes associated with the \( S \) gene. The two common chromosomes are \( DH \) and \( SL \) as before, but \( k = 0.8 \) and the relative population fitness increases to 0.958. With increasing \( r \) the \( D \) allele decreases, and with \( r \) greater than about 0.3 it disappears and segregation becomes Mendelian.

Fig. 5 shows the same information in graphical form, except that in this case the modifier is dominant. In the upper half, we see that \( k \) increases when \( r \) is small, becoming 0.9, the value for a \( DH/SL \) heterozygote, when \( r = 0 \). In contrast, if the modifier is on an independent chromosome or is loosely linked, it never increases. In the lower part of the graph, we see that a linked modifier reducing the \( k \) value increases, leading to a reduced \( \bar{k} \). With loose linkage, the \( D \) allele slowly disappears and \( \tilde{k} \) approaches 0.5. (It is not apparent from the graph but after a longer time the \( r = 0.5 \) line crosses the others and eventually reaches 0.5.)

Four conclusions emerge from these examples and from the more general theory.

1. A rare, tightly-linked modifier that increases \( k \) will be coupled to the distorting chromosome and will increase in the population. The average \( k \) will increase and the population fitness will decrease.

2. A new, unlinked or loosely linked modifier that increases \( k \) will not increase, and the mean \( k \) stays as before.

3. A new, tightly-linked modifier that decreases \( k \) will be coupled with the sensitive chromosome and will increase in the population. The mean \( k \) will decrease and the population fitness increases.

4. A new, unlinked or loosely linked modifier that decreases \( k \) will increase, thereby lowering the mean \( k \).

Conclusions 1 and 3 are intuitively reasonable. They were pointed out early (27,29). It is also reasonable that a
Table 1. The effect of a modifier that changes the k value at the distorting, (D,S), locus

<table>
<thead>
<tr>
<th>r</th>
<th>k₁</th>
<th>k₂</th>
<th>k₃</th>
<th>Equilibrium frequencies</th>
<th>Equilibrium values</th>
<th>( \frac{w}{k} )</th>
<th>( \frac{s}{k} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( k_{DH} )</td>
<td>( k_{DL} )</td>
<td>( k_{SL} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial frequencies→</td>
<td>0.01</td>
<td>0.40</td>
<td>0.01</td>
<td>0.58</td>
<td>0.824</td>
<td>0.700</td>
<td>0.595</td>
</tr>
<tr>
<td>0.00</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td>0.65</td>
<td>0.00</td>
<td>0.00</td>
<td>0.35</td>
</tr>
<tr>
<td>0.05</td>
<td>0.37</td>
<td>0.21</td>
<td>0.03</td>
<td>0.40</td>
<td>0.674</td>
<td>0.770</td>
<td>0.632</td>
</tr>
<tr>
<td>0.10</td>
<td>0.17</td>
<td>0.33</td>
<td>0.03</td>
<td>0.46</td>
<td>0.743</td>
<td>0.741</td>
<td>0.620</td>
</tr>
<tr>
<td>0.15</td>
<td>0.02</td>
<td>0.41</td>
<td>0.01</td>
<td>0.57</td>
<td>0.815</td>
<td>0.705</td>
<td>0.600</td>
</tr>
<tr>
<td>0.20</td>
<td>0.00</td>
<td>0.41</td>
<td>0.00</td>
<td>0.59</td>
<td>0.823</td>
<td>0.700</td>
<td>0.597</td>
</tr>
<tr>
<td>0.50</td>
<td>0.00</td>
<td>0.41</td>
<td>0.00</td>
<td>0.59</td>
<td>0.823</td>
<td>0.700</td>
<td>0.597</td>
</tr>
</tbody>
</table>

In each case the population starts at equilibrium with \( D/S \) heterozygotes having a \( k \) value of 0.7. In the upper half of the table a new rare modifier increases \( k \), in the lower half it decreases \( k \). The fitnesses of \( DD \), \( DS \), and \( SS \) are 0.1, 0.95, and 1.00, and \( r \) is the proportion of recombination between the distorting and modifier loci. The 'equilibrium' values were obtained by iterating Equations 4 until the frequencies no longer changed.

![Fig. 5. Change in the value of k as a result of a dominant modifier increasing its value (upper part) and decreasing it (lower part). The recombination between the distorting locus and the modifier is r.](image)

mutation that arises in the region between the drive and modifier loci that decreases the amount of crossing over between them will increase. Specifically an inversion will have this effect, so the large number of inversions in the SD system is no surprise.

The most striking, and at first sight surprising result comes from the asymmetry of conclusions 2 and 4. An unlinked modifier increases only if it depresses \( k \). It never increases \( k \) but may decrease it. Thus, in a species with a large number of chromosomes or a long linkage map, meiotic drive systems will tend to be suppressed by unlinked modifiers.

It is this principle that I think is mainly responsible for keeping the Mendelian system honest. It is perhaps to be expected that among unlinked modifiers of SD found in natural populations, those that reduce \( k \) tend to have a higher frequency than their alleles, as appears to be the case. (9)

An Intuitive ‘Grandchild’ Argument

Although the algebra is clear, it is not intuitively obvious that unlinked modifiers should increase if they reduce \( k \) but decrease if they enhance it. What’s in it for the modifier? If a modifier decreases the degree of distortion it has no more progeny than if it had been in a heterozygote with a high degree of distortion. So, where is the selection on the modifier?

A very neat statement comes from Ilan Eshel (35). It is analogous to the ‘grandchild’ argument often used to explain evolution of the sex ratio (38,39). First, note that in order for both \( D \) and \( S \) to coexist, the drive advantage of \( D \) must be balanced by a greater average fitness of the \( S \) allele. If there are two kinds of heterozygotes with different \( k \)'s, both kinds will contribute the same number of progeny (since the degree of distortion affects only the ratio of the two kinds of progeny, not the total number); but the one with the lower \( k \) will contribute more \( S \) chromosomes, which on the average cause fitter progeny than those receiving \( D \) chromosomes. Thus the parent with the lower \( k \) value will have a larger number of grandprogeny.

Since the grandparent with the lower \( k \) has the most grandprogeny, it will contribute more genes to future generations than one with a higher \( k \). Hence modifiers that lower \( k \) will increase. But, such modifiers must be independent of the \( D \) and \( S \) genes or they will be co-opted by the drive mechanism itself. Thus, there will be
a general tendency, provided the requisite independent modifiers exist, for a population to evolve toward Mendelism.

Why then isn’t a system like SD in Drosophila or the t system in mice obliterated by unlinked modifiers. And why are new systems being discovered(40)? A clue is offered by the fact that selection for linked k-enhancers is stronger than for k-depressors, especially unlinked ones, as illustrated by their rates of change (Fig. 5). Thus, a few linked enhancers may sometimes outweigh a larger number of depressors. In the SD system there is the SD chromosome and its linked enhancers striving to increase k, the homologous chromosome in which there is selection for insensitivity, and a host of unlinked modifiers tending to reduce the degree of distortion. SD chromosomes are so rare in natural populations that there is little opportunity for selection of unlinked modifiers.

Mendelian Inheritance

There has been much discussion of the evolutionary advantages of Mendelism. Most arguments deal with recombination rather than segregation, but see Charlesworth(41). There is the standard argument that the system of gene-testing works best when each gene is given a fair test in combination with many others, as in a factorial experiment. Cheating genes lower the efficiency of the system by causing less fit alleles sometimes to prevail over more fit ones.

The argument in this paper provides a mechanism for selection of modifiers that favor a 1:1 Mendelian segregation. A similar argument has been given by Leigh(42). These are strictly individual selection mechanisms and should therefore be warmly welcomed by those evolutionists who prefer to invoke group selection only as a last resort.

A half-century ago Haldane(1) pondered the question of conflict between gametic and zygotic selection. The quote at the beginning of this article is an example of his concern. No doubt he would have had something to say about meiotic drive, had the phenomenon been recognized at the time.

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References

PROBLEMS AND PARADIGMS


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