Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

The Ultraselfish Gene

In 1957 L. Sandler and E. Novitski published an article entitled "Meiotic drive as an evolutionary force" in which they wrote:

> As the study of the genetics of higher organisms becomes more precise and extensive, an increasing number of cases is found in which heterozygotes of certain constitutions fail to produce the two kinds of gametes with equal frequency. Such a pattern of behavior will drastically alter frequencies of alleles in a population; where such a force, potentially capable of altering gene frequencies, is a consequence of the mechanics of the meiotic divisions, we suggest that the name *meiotic drive* be applied.

They called attention to the excess of daughters produced by "sex ratio" males of *Drosophila pseudoobscura,* preferential segregation of knobbed chromosomes in maize (caused by neocentromeres, which are selectively included in the egg nucleus), nonrandom disjunction in heteromorphic chromosomes in female *Drosophila melanogaster,* and the excess of progeny carrying *t* alleles from male mice.

The meiotic drive paper appeared in the spring of 1957 at about the time Sandler had obtained a fellowship to work at the University of Wisconsin. Coincidentally, and unknown to him, Y. Hiraizumi had just discovered a case of extreme meiotic drive in a natural population of *D. melanogaster.* The two of them made a superb team and in the next few years they worked out the basic phenomenology of *Segregation distortion* (*SD*), as they named it.

In the intervening three decades a great deal more has been learned about meiotic-drive systems and, on January 6–8 of this year, a conference on this subject was held at the University of Hawaii. The organizers were T. Lyttle, D. Perkins and T. Prout. The success of the conference can be attributed to its narrow focus on transmission-ratio distortion and to the knowledge and active interest of the roughly 50 attendees. To the regret of the participants, neither Novitski nor Sandler was able to attend. Both were sorely missed. Especially distressing to his many friends and admirers was the death of Larry Sandler only a few months earlier. He had been one of the original organizers of the Conference. Several of the participants spoke of his scientific ingenuity, his depth and breadth of knowledge and his friendly guidance.

The subject matter was broader than originally encompassed by the term *meiotic drive.* The discussions included a plethora of mechanisms by which a genetic entity is able to increase in the population without regard to, or in spite of, its effect on the fitness of the host organism. Some of the examples were: B chromosomes in a large number of plants, gametocidal genes in cereals, Spore-killer in Neurospora, sex-ratio genes in mosquitos, sex-ratio factors in parasitic hymenoptera, preferential transmission of structurally abnormal chromosomes in *D. melanogaster,* and chromosome drive in *Lucilia cuprina.* The mechanisms are diverse but the common element is that, in each case, the driven entity is preferentially transmitted to the next generation. For example, some B chromosomes accomplish this by regular nondisjunction followed by nonrandom inclusion in the sperm nucleus destined to fuse with the egg nucleus. The systems range from preferential segregation in maize, which is meiotic drive by the strictest definition, to parasitic microorganisms. Ideas and data flowed freely during the conference. The origins of some are identified in parentheses below.

The past year has been one of great progress in the *SD* complex in *D. melanogaster* (B. Ganetzky). As shown in Figure 1, the system includes (besides numerous modifiers) *Segregation distorter* (*Sd*), Responder (*Rsp*) and *Enhancer* (*E*(*SD*), here designated

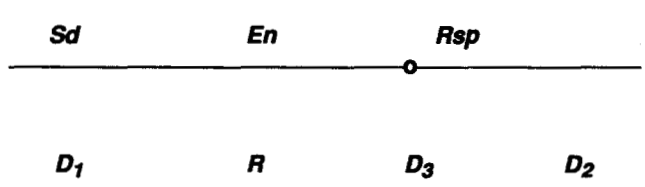

Figure 1.—Rough maps of the gene orders for the *SD* region in Drosophila (upper) and the *t* region in the mouse (lower). The symbols are: *Sd, Segregation distorter*; *En, Enhancer*; *o, centromere*; *Rsp, Responder*; D_1, D_2, D_3, *distorters*; *R, Responder.*

En). *Responder* may be sensitive (*Rsp*^{s}) or insensitive (*Rsp*^{i}). In the presence of *Sd*, sperms carrying *Rsp*^{s} fail to develop normally, leading to distorted transmission ratios. *En* is similar to *Sd*; each is independently capable of causing dysfunction of *Rsp*^{s} sperms but their effect is greater when they are combined (R. TEMIN). The driven chromosome found in natural populations is *Sd En Rsp*^{i}. Being insensitive, it has no dysfunctional effect on its own sperm, but in heterozygous males it is highly destructive to sperms carrying *Rsp*^{s}.

The *t* system in mice is quite similar, as can be seen in Figure 1 (M. LYON, D. BENNETT). The three distorter alleles, D_1, D_2, and D_3, are comparable to *Sd* and *En* in their cumulative effect. In the presence of one or more distorter alleles, sperms containing R^+ are dysfunctional while sperms carrying *R* are resistant. Thus, R^+ is comparable to *Rsp*^{s} and *R* to *Rsp*^{i}. In both systems the responder locus exists in various degrees of responsiveness. And, in both systems there are crossover-suppressing inversions. This hints that the special property of distorter genes in both mouse and Drosophila is not the specific nature of their product, but rather their tight linkage to a responder locus.

Both *Sd* and *Rsp* have been cloned. *Sd*$^+$ and *Sd* chromosomes have 7-kb and 12-kb *Eco*RI fragments, respectively, and detailed restriction mapping reveals that *Sd* carries a duplicated segment. There is a 4.2-kb *Sd*-specific transcript (P. POWERS). The structure of *Responder* turns out to be particularly suggestive. It was first shown to be divisible (T. LYTTLE), then multiple (S. PIMPINELLI), and finally to comprise repeated 120-bp units (C.-I. WU). The sensitivity increases with the number of repeats up to several hundred for "supersensitive" chromosomes. Although it does not reveal a specific mechanism of *Sd-Rsp* interaction, this molecular insight encourages the hope that such knowledge will be forthcoming. The underlying cause of sperm dysfunction remains obscure in both Drosophila and mouse.

The sex-determining systems of hymenoptera, where diploids are female and haploids male, are a particularly inviting target for entities that distort the sex ratio. A rather small sample from a wild population of the parasitic wasp, *Nasonia vitripennis* (familiar to genetic oldsters as *Mormoniella*), yielded no fewer than three different systems. In each case the intruding entity shifts the sex ratio in the direction that furthers its own perpetuation. "Son-killer" is a maternally transmitted bacterium that causes the unfertilized eggs not to hatch, thus producing all-female progeny. The maternally transmitted "Maternal sex ratio" (MSR) induces the inseminated female, which has control over whether or not eggs are fertilized, to fertilize all her eggs, producing only female offspring. MSR differs from Son-killer in that there is no egg lethality. "Paternal sex ratio" (PSR) causes degeneration of the paternal chromosomes so that all the progeny are male. It had previously been thought that the causative agent was extrachromosomal. It turns out, however, that it is a supernumerary chromosome that destroys all paternally derived chromosomes except itself (J. WERREN). In this way the fratricidal chromosome perpetuates itself by causing the production of male offspring, which carry it to the next generation.

Meiotic drive leads to all sorts of interesting evolutionary questions. It is easily shown that PSR can increase only if the proportion of eggs fertilized is greater than ½; this happens when MSR is present. The *t* region in the mouse regularly carries a number of lethals, in contrast to a small number or none in *SD* chromosomes of Drosophila. There is an obvious advantage to the population in converting useless sterile males into embryonic lethals. But how can one explain this without committing the sin of invoking group selection? The clue may lie in mice being litter-bearing with possible reproductive compensation and having a demic population structure; these might favor some form of kin selection (B. CHARLESWORTH). Mice also seem to have behavioral modifications that weaken the *t*-locus drive system; females appear to prefer +/+ males (S. LENNINGTON). Could such kinds of behavior be found with other systems? Meiotic-drive systems are a fertile field for population genetics theory; many results are counter-intuitive to one used to thinking in Mendelian terms, especially in linked multilocus systems (M. FELDMAN). One particularly interesting result is that drive-reducing modifiers are more readily incorporated into the population when they are independent of the drive system. Thus, organisms having a large number of chromosomes with individually long linkage maps would be those most capable of tolerating drive systems. An autosomal drive system that is otherwise harmless, or nearly so, can be carried to fixation with little permament harm. This is not true for a driven *Y* chromosome, which can only lead to extinction through an excess of males. Is hedging against such a disaster a reason for the genetic inertness of *Y* chromosomes (W. HAMILTON)?

A deletion of *Sd* behaves like *Sd*$^+$ and a deletion of *Rsp* is insensitive. Neither locus is required for normal development. Yet it seems likely that *Sd*$^+$ has some function; this notion is strengthened by finding the 7-kb restriction pattern in *D. simulans*. But such a function may have nothing to do with segregation distortion. Population studies of the *SD* system have been inhibited by the absence of an overt phenotype. The necessity for progeny testing has made experiments very labor-intensive. Recent molecular knowledge makes it possible to determine the genotypes of individual flies. It seems obvious that *Rsp*^{s} must

have a selective advantage compared to *Rsp*^{i}; otherwise it would not be as common as it is in natural populations. Only with molecular methods has it been feasible to test this, and early studies with population cages seem to bear out the conjecture. In theory, the *SD* system produces the kind of cyclical trajectories of chromosome frequency change that have long fascinated population ecologists. But experimental tests of this depend on the kinds of precise measures of fitnesses of the different components that have only recently become feasible.

What is the conclusion from such a Conference? I think it is this: Mendelism is a magnificent invention for fairly testing genes in many combinations, like an elegant factorial experimental design. Yet it is vulnerable at many points and is in constant danger of subversion by cheaters that seem particularly adept at finding such points.

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LITERATURE CITED

Sandler, L., and E. Novitski, 1957 Meiotic drive as an evolutionary force. Am. Nat. **41:** 105–110.