Letter to the Editor

Measuring Meiotic Drive

Leonard G. Robbins,* Gioacchino Palumbo,† Silvia Bonaccorsi‡ and Sergio Pimpinelli†,‡

**Genetics Program and Department of Zoology, Michigan State University, East Lansing, Michigan 48824-1312, †Istituto di Genetica, Università di Bari, 70126 Bari, Italy, ‡Dipartimento di Genetica e Biologia molecolare, Università di Roma "La Sapienza," 00185 Roma, Italy*

Manuscript received October 21, 1995
Accepted for publication October 27, 1995

LAURENCE HURST's (1996) letter re-examines our data on the effect of *Stellate* copy number on the meiotic parameters of *crystal*$^-$ (= *Su(Ste)*$^-$) males (PALUMBO *et al.* 1994). In our analysis, we found a tight correlation of fertility and disjunction with *Stellate* copy number, with both being normal at low copy numbers. In contrast, we found only a weak correlation of meiotic drive and *Stellate* copy number, with substantial sperm lethality projected to exist even at *Stellate* copy number = 0. We argue that the absence of *crystal*, not the presence of *Stellate*, is the proximate cause of drive in *crystal*$^-$ males. HURST argues that the data support the hypothesis (HURST 1992) that *Stellate* causes drive.

To some extent this difference reflects our focus on meiotic mechanism, and HURST's focus on evolutionary mechanism. HURST may have also misconstrued the parameters used in our analysis. R_X and R_Y are not the proportions of *X*- or *Y*-bearing progeny. They are measures of the effects of having an *X* or *Y* chromosome in a sperm. In other words, $1 - R_X$ is the sperm lethality caused by an *X* chromosome, whether or not a *Y* is present. These parameters follow the formulation of MCKEE (1984). That is, for P_{XY} = the probability of *X*-*Y* disjunction, R_X = the recovery of *X*-bearing sperm, and R_Y = the recovery of *Y*-bearing sperm, the probabilities of the surviving sperm are $X = {}^1/_2P_{XY}R_X$, $Y = {}^1/_2P_{XY}R_Y$, $XY = {}^1/_2(1 - P_{XY})R_XR_Y$, and $0 = {}^1/_2(1 - P_{XY})$. R_X is neither the proportion of all *X*-bearing progeny, $(X + XY)/(X + Y + XY + 0)$, nor the proportion of *X*-only progeny, $X/(X + Y + XY + 0)$, but is $\sqrt{(X \cdot XY)/(Y \cdot 0)}$. R_X and R_Y measure the separate effects of the *X* and *Y* chromosomes on sperm survival and are independent of the frequency of disjunction, which is measured by P_{XY}. We did find a highly significant correlation of *Stellate* copy number with sperm lethality, and contrary to HURST's assertion, the slope is in the expected direction; increased *Stellate* copy number gives lower recoveries. However, we also found the following: (1) that the slope is shallow; (2) that the correlation explains only a small fraction of the variation; and (3) that substantial sperm lethality would remain even if *Stellate* copy number were zero. The *Y* does have a more severe effect on survival (*i.e.*, $R_Y < R_X$), but that too is true at all *Stellate* copy numbers, including zero. This is not a "result of two antagonistic forces, one of which is *X* versus *Y* meiotic drive." Had our measure been the proportion of *X*-bearing sperm, $(X + XY)/(X + Y + XY + 0)$, we would indeed have compounded "the recovery of *XY* sperm with *X*-only sperm" and we would in fact have tested whether *Stellate* is "a meiotic drive gene that acted to inhibit sperm not containing it." That was not the measure used and that was not the hypothesis tested.

HURST presents plots and conventional, continuous-variable regression analyses of two other metrics: the proportion of *X*-bearing sperm among disjunctional products

$$\frac{X}{X + Y} = \frac{R_X}{R_X + R_Y},$$

and the proportion of *XY* sperm among nondisjunctional products

$$\frac{XY}{XY + 0} = \frac{R_XR_Y}{1 + R_XR_Y}.$$

In terms of meiotic mechanism, these compound the effects of the *X* and *Y* chromosomes, but they do focus attention on chromosome transmission. Nevertheless, discrete-variable, maximum likelihood analysis reveals the same problems for these measures as for R_X and R_Y.

Likelihood analysis has two advantages. First, it takes account of sample size and is therefore more powerful. Second, we can not only ask whether a correlation is significant, we can also ask whether it explains a substantial part of the variation—a correlation can be both statistically significant and, at the same time, unimportant. The results of this analysis for all four measures of drive are shown in Figure 1. We agree with HURST that these measures are significantly correlated with *Stellate* copy number. Because maximum-likelihood estimates use all of the data, our estimates of the slope and inter-

Corresponding author: Leonard G. Robbins, Genetics Program, S306 Plant Biology, Michigan State University, E. Lansing, MI 48824-1312. E-mail: 21675mgr@msu.edu

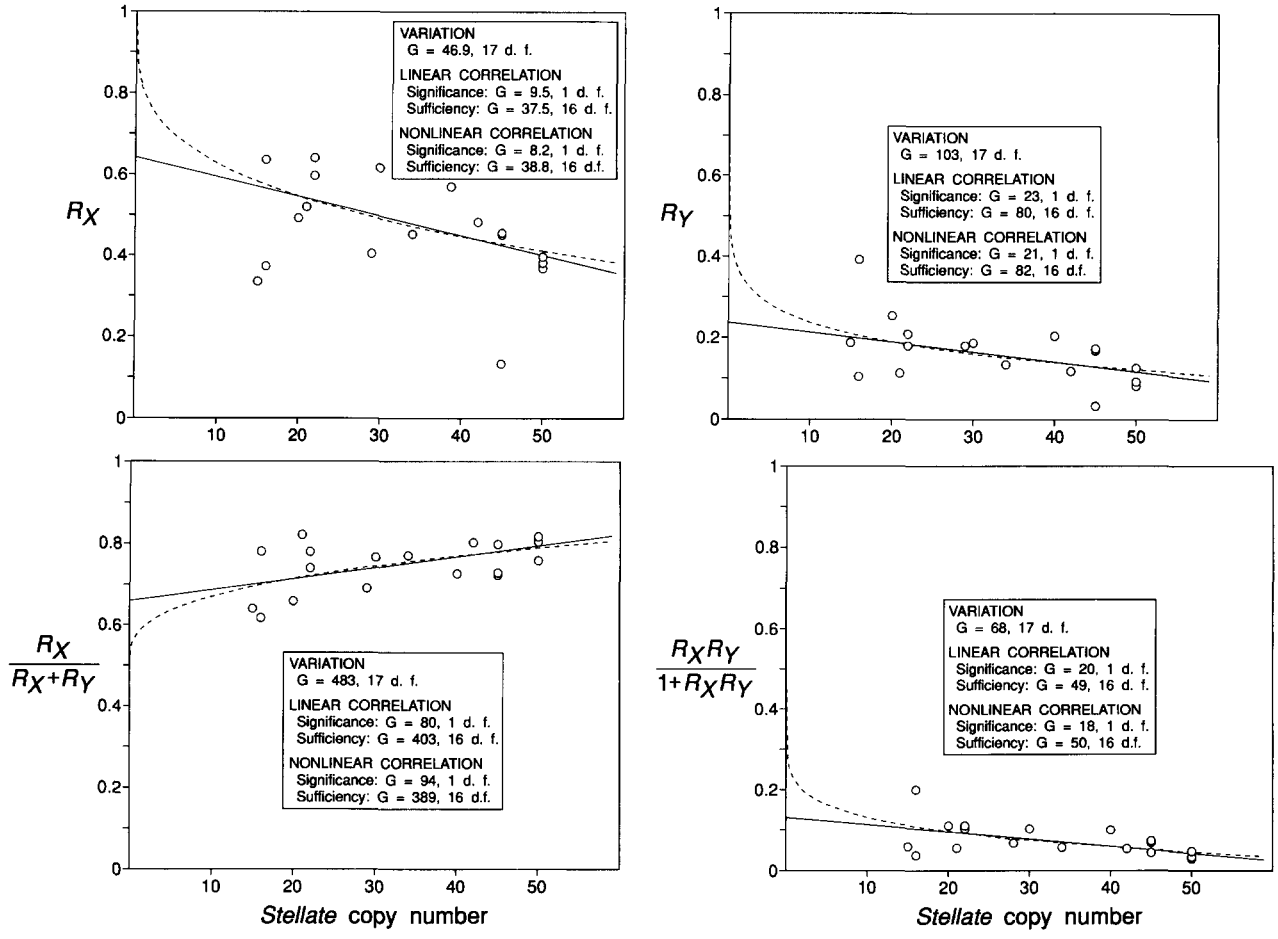

FIGURE 1.—Relationship of *Stellate* copy number to parameters of meiotic drive. Linear and nonlinear correlations were evaluated using discrete multivariate analysis for the two measures of meiotic drive, R_X and R_Y, used in PALUMBO *et al.* (1994) and for the two measures, $X/(X + Y) = R_X/(R_X + R_Y)$ and $XY/(XY + 0) = R_XR_Y/(1 + R_XR_Y)$, used by HURST. The linear correlations (———) are *parameter* = m(*Stellate* copy number) + n, and the nonlinear correlations (-----) are R_X or $R_Y = 1 + m$(*Stellate* copy number)^n and $R_X/(R_X + R_Y)$ or $R_XR_Y/(1 + R_XR_Y) = 0.5 + m$(*Stellate* copy number)^n. The variation in each of these parameters is highly significant ($P < 0.005$), as are the correlations with *Stellate* copy number. Both the linear and nonlinear correlations, however, explain only a small fraction of the variation in any of the parameters.

cept differ slightly from his [*e.g.*, for $R_X/(R_X + R_Y)$, slope = 0.0027, intercept = 0.66]. Because the G test takes account of sample size, we can see that there is no need for HURST's concern that the level of significance might be marginal. Nevertheless, the correlations of $R_X/(R_X + R_Y)$ and $R_XR_Y/(1 + R_XR_Y)$ with *Stellate* copy number are just as shallow as those of R_X and R_Y, they also leave most of the variation unexplained, and drive does not disappear in the absence of *Stellate*.

Given a linear response, substantial drive against the *X*, substantial drive against the *Y* (and substantial drive against autosomes, an observation not addressed by HURST's hypothesis) would occur in *crystal*$^-$ males even in the absence of *Stellate*. HURST's interpretation of the correlation of drive with *Stellate* copy number thus requires an assumption that there is a nonlinear response between a *Stellate* copy number of zero and the actual data points—if *Stellate* is the drive inducer, absent *Stellate* there should be no drive. No such assumption is required for the effect of *Stellate* copy number on disjunction since a linear correlation of disjunction with *Stellate* copy number not only explains the vast majority of the variation, but nondisjunction reaches zero well before copy number does (PALUMBO *et al.* 1994).

HURST invokes "the law of diminishing returns" as an origin of the nonlinearity, but provides no analysis of this assumption. It is not difficult, however, to extend the maximum-likelihood analysis to a nonlinear correlation wherein there is no drive when *Stellate* copy number = 0 and there is a decreasing effect of successive copy number increments. The results of that analysis are also shown in Figure 1. Whether for R_X, R_Y, $R_X/(R_X + R_Y)$, or $R_XR_Y/(1 + R_XR_Y)$, the nonlinear correlation is insensibly different from the linear. Without experimental support, this assumption remains *ad hoc*; it is needed only if HURST's hypothesis is assumed to be true.

Although a differential effect of *Stellate* on survival of *Y*-bearing sperm is a necessary condition of HURST's hypothesis, it is, as HURST carefully notes, not a sufficient condition of the hypothesis. It is also not a suffi-

cient explanation of the data. We do not infer that the basic effect of *crystal*$^-$ on sperm survival is necessarily mediated by a locus linked to *Stellate,* but suggest that if drive involves an interaction of *crystal*$^-$ with another locus at all, *Stellate* is not the principal participant. A nearby site previously identified by McKee because of its interaction with the ribosomal RNA genes (rDNA; McKee 1987) may be a candidate. In any case, our basic conclusion, that the drive is caused by *crystal*$^-$ rather than by *Stellate,* is "tentative" only because it includes a projection to *Stellate* copy number = 0, a situation that has yet to be experimentally tested.

As further support for ascribing importance to the correlation of $R_X/(R_X + R_Y)$ and *Stellate* copy number, Hurst notes that its direction is contrary to a definition of drive that he ascribes to Hardy *et al.* (1984), but is in accord with the direction predicted by his hypothesis. From that definition, that "sperm with few and small chromosomes were preferentially recovered," and from the slightly smaller size of the *Drosophila melanogaster Y,* Hurst infers that "one might expect an increase in the relative proportion of *Y*-bearing sperm as *Stellate* copy number goes up." As Hurst notes, in *crystal*$^-$ males the converse is observed. Hardy *et al.* did not, however, decompose their data into disjunctional and drive parameters, and neither they nor anyone else that we know of has yet tested for an effect of chromosome size unmuddied by differences in chromatin content. In *crystal*$^-$ males, the *Y* chromosome causes more sperm lethality than does the *X* at all *Stellate* copy numbers. A substantially greater sperm-lethal effect of the *Y* chromosome is also a notable property of the drive caused by rDNA deficiencies (McKee 1984). Given that, would Hurst posit that evolution of the rDNA inter-genic spacer (McKee *et al.* 1992), was also a suppressive response to *Stellate*-induced meiotic drive?

Meiotic mechanism and evolutionary mechanism are not necessarily the same thing however. Although absence of *crystal,* rather than presence of *Stellate,* appears to be the cause of drive in *crystal*$^-$ males, *Stellate* copy number might nevertheless be driven to increase. R_Y and R_X are better measures for discerning meiotic mechanism, but $X/(X + Y)$ has special interest for understanding *Stellate*'s evolution because distortion of the recovery of *XY* and *nullo* sperm does not alter the relative frequency of the *X.* Thus, the increasing frequency of *X*-bearing sperm among regular offspring as *Stellate* copy number increases would favor copy number increases that might be countered by increasing *crystal* dose. Increased *Stellate* copy number, however, is even more strongly correlated with decreased fertility. Just where the balance lies between increased frequency of *Stellate*-bearing *X* chromosomes because of drive and their elimination because of infertility is unlikely to be resolved by qualitative arguments.

Both *crystal* and rDNA deficiencies cause profound and complex disruptions of meiosis. This complexity is reflected for *crystal*$^-$ in the rather different statistical properties of fertility and disjunction, on the one hand, and drive, on the other. Hurst singles out the weakest of the correlations. We may have overemphasized its weakness. Perhaps it would be better to simply say that *crystal* deficiencies and rDNA deficiencies both cause drive and avoid conjectures about gene interactions until they are experimentally demonstrated.

We thank Peter Crawley, Thomas Friedman and Ellen Swanson for their critiques of a draft of this letter. This work was supported by National Science Foundation grant MCB-9305846 and by grants CR. NO.91.00012PF99 of progetto finalizzato "Ingegneria Genetica" of the Italian National Research Council and Progetti di ricerca MURST 40%.

LITERATURE CITED

Hardy, R. W., D. L. Lindsley, K. J. Livak, B. Lewis, L. Siversten *et al.,* 1984 Cytogenetic analysis of a segment of the *Y* chromosome of *Drosophila melanogaster.* Genetics **107:** 591–610.

Hurst, D. L., 1992 Is *Stellate* a relict meiotic driver? Genetics **130:** 229–230.

Hurst, D. L., 1996 Further evidence consistent with *Stellate*'s involvement in meiotic drive. Genetics **142:** 641–643.

McKee, B., 1984 Sex chromosome meiotic drive in *Drosophila melanogaster* males. Genetics **106:** 403–422.

McKee, B., 1987 *X-4* translocations and meiotic drive in *Drosophila melanogaster* males: role of sex chromosome pairing. Genetics **116:** 409–413.

McKee, B. D., L. Habera and J. A. Vrana, 1992 Evidence that intergenic spacer repeats of *Drosophila melanogaster* rRNA genes function as *X-Y* pairing sites in male meiosis, and a general model for achiasmatic pairing. Genetics **132:** 529–544.

Palumbo, G., S. Bonaccorsi, L. G. Robbins and S. Pimpinelli, 1994 Genetic analysis of *Stellate* elements of *Drosophila melanogaster.* Genetics **138:** 1181–1197.

Communicating editor: T. W. Cline