Letter to the Editor

Resurrecting MULLER's Theory of HALDANE's Rule

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HALDANE's rule is one of the most enduring empirical generalizations in evolutionary biology. It states that "if only one sex is sterile, rare or inviable among species hybrids, it is the heterogametic sex" (HALDANE 1922; COYNE 1994). This rule holds both in situations where males are the heterogametic sex (*e.g.*, in dipterans and mammals) (HALDANE 1922; GRAY 1954; BOCK 1984) and in situations where the females are the heterogametic sex (*e.g.*, in birds and lepidopterans) (HALDANE 1922; GRAY 1954). A compilation of interspecific hybridization data in *Drosophila*, mammals, birds and *Lepidoptera* by WU and DAVIS (1993) shows that only 19 out of 359 cases violate HALDANE's rule. Such a striking general phenomenon has been known for more than 70 years, but its genetic basis, which may be crucial to the understanding of the process of speciation, is still unclear.

The search for the genetic basis of HALDANE's rule started when the rule was formulated, and many explanations have been offered since then. These include, to mention a few, *X*-autosome interactions (DOBZHANSKY 1937a,b; MULLER 1940, 1942), *X*-*Y* interactions (COYNE 1985), the faster accumulation of recessive, adaptive substitutions on sex chromosomes than autosomes (CHARLESWORTH *et al.* 1987; COYNE and ORR 1989) and meiotic drive theories (FRANK 1991; HURST and POMIANKOWSKI 1991). None of these provides a completely satisfactory explanation (COYNE 1992; WU and DAVIS 1993). This has led to the proposal that HALDANE's rule is a coincidence of multiple causes and does not have a unitary explanation (ORR 1993a; WU and DAVIS 1993). Most recently, TURELLI and ORR (1995) generalized ORR's (1993b) treatment of a dominance theory that explains both HALDANE's rule and other related phenomena. The dominance theory is not a new theory but a mathematical expression of MULLER's *X*-autosome interaction hypothesis proposed half a century ago (MULLER 1940, 1942).

In this note, I wish to argue that the previous failure in finding a satisfactory explanation is the result of

rejecting a correct hypothesis, namely MULLER's *X*-autosome interaction hypothesis which has been discarded together with DOBZHANSKY's *X*-autosome imbalance theory in the recent literature. I will also provide a simple additive model and experimental data supporting MULLER's theory.

***X*-autosome interaction hypothesis revisited:** For the past 50 years, the *X*-autosome interaction model has been the traditional explanation of HALDANE's rule. It includes two distinct but related hypotheses. One is the *X*-autosome imbalance hypothesis proposed by DOBZHANSKY (1937a,b). Another is the *X*-autosome interaction hypothesis proposed by MULLER (1940, 1942). The *X*-autosome imbalance explanation is based on the assumption that "many species have a balance of genes in the *X* chromosome and the autosomes peculiar to themselves and different from other species" (DOBZHANSKY 1937a). This assumption is supported by the observation of frequent rearrangements (fusion, fission, translocation, deletion and duplication) of chromosomes (WHITE 1973, 1978) and chromosome segments (DOBZHANSKY and TAN 1936a,b; DOBZHANSKY 1937b) between the *X* chromosome and the autosomes among many *Drosophila* species. For convenience, I use male for the heterogametic sex and female for the homogametic sex. As female hybrids have a complete set of autosomes and an *X* chromosome from each parental species, the *X*-autosome balance remains undisturbed. In male hybrids, however, the *X* chromosome corresponding to the paternal set of autosomes is missing, so the genic balance between the autosomes and the *X* chromosome is perturbed and causes sterility or inviability in hybrid males (heterogametic sex).

MULLER's (MULLER 1940, 1942) *X*-autosome interaction hypothesis, which has often been lumped with DOBZHANSKY's *X*-autosome imbalance hypothesis (WU and DAVIS 1993; ORR 1993a), states that either the absence of some sex-linked genes that are necessary complements for those on the autosomes or the expression of some sex-linked deleterious genes in the heterogametic sex can lead to sterility or inviability. It is clear that MULLER's hypothesis emphasizes the importance of *X*-linked recessive incompatible genes in causing hybrid sterility and inviability of the heterogametic sex (incom-

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patibility at the gene level), whereas DOBZHANSKY's X-autosome imbalance is concerned with incompatibility (imbalance) at the chromosomal level. They are two distinct hypotheses implying different underlying genetic causes.

However, there are similarities between the two hypotheses. Both of them involve interactions between genes on the X chromosome and the autosomes and emphasize the difference in copy number of the X chromosome in males and females. Therefore some tests are often applicable to both of them, and they are often accepted or rejected together. As the X-autosome imbalance can be traced to the gene level, it can be considered as one particular type of the recessive deleterious interactions specified in MULLER's hypothesis. MULLER's X-autosome interaction hypothesis is, therefore, more general and inclusive than the X-autosome imbalance hypothesis.

The X-autosome imbalance hypothesis was tested by COYNE (1985) in species pair *Drosophila simulans* and *D. mauritiana* (or *D. sechellia*). He crossed *D. simulans* females with attached-X chromosomes to *D. mauritiana* (or *D. sechellia*) males and obtained hybrid females, homozygous for the X chromosomes from one species (*D. simulans*) and heterozygous for the autosomes from both parental species. These females have the same degree of X-autosome imbalance as the sterile hybrid males from this species pair, but are nevertheless fertile contrary to the prediction of the X-autosome imbalance hypothesis. The X-autosome imbalance hypothesis was then rejected (COYNE 1985). The result of the attached-X experiment has also been used to reject MULLER's X-autosome interaction hypothesis (COYNE and ORR 1989), as the hybrid females were fertile when their X chromosomes were made homozygous from one species (unmasking of the recessive X-linked alleles). This inference, however, has been challenged by several authors. First, since we know that all the chromosomes of the three species used in the attached-X experiment are homosequential (LEMEUNIER and ASHBURNER 1984), the translocation of any chromosome or chromosome segment between X and autosomes postulated in DOBZHANSKY's X-autosome imbalance hypothesis does not exist. So it is clear beforehand that X-autosome imbalance does not apply to these species pairs. Second, such closely related species pairs may not have evolved hybrid female sterility genes yet (ORR 1993b). As sterility genes (unlike inviability genes) tend to affect one sex only, the species pairs with hybrid male sterility may not have also picked up additional X-linked recessives causing hybrid female sterility. Thus, it is not surprising that hybrid females carrying both Xs from the same species remain fertile (ORR 1993b). Finally, ZOUROS (1989) argued that although X-autosome imbalance (or interaction) does not cause hybrid female sterility, it does not follow that hybrid male sterility is also not caused by such an imbalance (or interaction), because the devel-

opmental pathways involved in male and female fertility may be very different (see also WU and DAVIS 1993). WU and DAVIS (1993) suggested that a better test of the hypothesis would examine hybrid inviability, because the developmental pathways involved in male and female inviability are likely to be more similar than those involved in male and female sterility.

As suggested by WU and DAVIS (1993), a more appropriate test of the X-autosome interaction hypotheses can be devised. Using the same method as COYNE (1985), ORR (1993a) tested the inviability aspect of the X-autosome interaction hypotheses in the species pair *D. simulans* and *D. melanogaster* (or *D. teissieri*) (see also HUTTER *et al.* 1990). The results of the test are exactly what are predicted by the X-autosome imbalance and MULLER's X-autosome interaction hypotheses, *i.e.*, hybrid females, homozygous for the X from one species, are as inviable as the hybrid F₁ males bearing the same X. As the results of this test contradict those of the previous test on sterility, ORR (1993a) interprets his results as due to the composite nature of HALDANE's rule (WU and DAVIS 1993), *i.e.*, the X-autosome interaction hypothesis explains the inviability aspect but not the sterility aspect of HALDANE's rule. However, I would consider an alternative explanation to be that his test provides strong evidence supporting MULLER's X-autosome interaction hypothesis. His data *per se* do not have any bearing on the composite nature of HALDANE's rule.

Recently BIDDLE *et al.* (1994) crossed fertile XO laboratory female mice of *Mus musculus musculus* to males of *M. spretus*. Among the hybrid offspring produced, the XX females were fertile and the XY males were sterile, as are regular hybrids between these two species. However, the XO hybrid females were completely sterile, as were their XY sibs. This experiment provides a third test of the X-autosome interaction hypotheses, and the result is exactly as predicted by the theories. The rationale of this test is the same as that of COYNE (1985) and ORR (1993a). Hybrid females are sterile when made hemizygous (or unbalanced) and recessive deleterious alleles are allowed to be expressed.

A logical explanation of HALDANE's rule: HALDANE's rule applies to heterogametic males as well as heterogametic females. The common basis of HALDANE's rule must therefore be connected not with sex, but with sex chromosomes. The differences of sex chromosomes between sexes is the logical starting place to explain why heterogametic sex is preferentially affected in hybrids. The first obvious difference is the presence of the Y chromosome (or the W chromosome) in heterogametic sex. Starting from this difference, we have the X-Y interaction hypothesis, which does not provide a general explanation for HALDANE's rule (JOHNSON *et al.* 1992; ZENG and SINGH 1993). The second major difference of sex chromosomes between sexes is haploidy in the heterogametic sex (hemizygous) and dip-

loidy in homogametic sex. The consequence of this difference is that both dominant and recessive sex-linked genes are expressed in the heterogametic sex and only dominant or partially dominant genes are expressed in the homogametic sex. In interspecific hybrids, only sex-linked recessive or partially recessive incompatible genes contribute to HALDANE's rule. Sex-linked dominant and autosomal incompatible genes (when not interacting with sex-linked genes) tend to affect both sexes and therefore do not contribute to HALDANE's rule. A simple explanation of HALDANE's rule is, therefore, that HALDANE's rule results from expression of some recessive sex-linked incompatible genes. In the hybrids of heterogametic sex, the sex-linked incompatible genes are incompatible with genes from alien autosomes or sex chromosome. The incompatibility can be sterility, inviability or any other disharmony causing loss of fitness such as the morphological abnormalities that follow HALDANE's rule in flour beetles (WADE and JOHNSON 1994; WADE *et al.* 1994).

This explanation is essentially the same as MULLER's X-autosome interaction hypothesis which has been mixed and "killed" together with DOBZHANSKY's X-autosome imbalance hypothesis (discussed above). The extension is that this explanation deals with not only the X-autosome interactions but also X-Y and Y-autosome interactions. This model is best described as the recessivity model of HALDANE's rule to reflect the recessive nature of deleterious genes expressed in heterogametic hybrids.

A simple additive model of MULLER's theory: ORR (1993b) noted the appeal of MULLER's recessivity model (see also COYNE 1994). He re-examined the model with a mathematical approach and showed that MULLER's model is valid only when the effects of the incompatible genes and their degrees of dominance are negatively correlated, *i.e.*, the alleles of larger effect on hybrid sterility or inviability are more recessive. An assumption which led ORR (1993b) to refute MULLER's original hypothesis is that the average degree of dominance of X-linked incompatible genes is 1/2 (ORR 1993b, p. 1608). This assumption is not imbedded in MULLER's hypothesis at all. MULLER (1940, 1942) clearly specified the recessive nature of hybrid sterility and inviability genes in two causes of deleterious effects of his theory. One is "absence of some sex-linked genes which are necessary complements for those on the autosomes," which implies recessive "loss-of-function" genes. The other is "expression of some sex-linked deleterious genes in heterogametic sex," which also implies recessivity. By invoking the recessivity and epistatic interactions of X-linked hybrid sterility and inviability genes, TURELLI and ORR (1995) relaxed ORR's assumption and proposed an epistatic model (the dominance theory), which shows that MULLER's theory holds when the average degree of dominance of the deleterious effects of incompatible alleles is smaller than one half. The addi-

tional assumption of an inverse relationship between the effects of the incompatible genes and their degrees of dominance is unnecessary. I have independently reached a very similar conclusion using a simple additive model.

Let k be the number of X-linked deleterious alleles affecting hybrid fitness, r_i and h_i , respectively, be the amount and the degree of dominance by which the i th allele lowers hybrid fitness. Assuming additivity across loci, the hybrid fitness, w , is then

$$w = 1 - \sum_{i=1}^k r_i h_i = 1 - k\bar{r}\bar{h} - k \text{cov}(r, h).$$

For male hybrids, the X-linked alleles behave as though completely dominant; therefore, $\bar{h} = 1$ and $\text{cov}(r, h) = 0$ so that the male hybrid fitness is $w_m = 1 - k\bar{r}$. For female hybrid fitness, the number of incompatible genes is twice as many as in hybrid males (in female, there are two X chromosomes each of which has the same probability of carrying deleterious genes), $2k$. So the female hybrid fitness is $w_f = 1 - 2k\bar{r}\bar{h} - 2k \text{cov}(r, h)$; therefore, the ratio of hybrid male to female fitness is

$$w_m/w_f = (1 - k\bar{r})/[1 - 2k\bar{r}\bar{h} - 2k \text{cov}(r, h)].$$

This ratio must be smaller than one to account for HALDANE's rule. $w_m/w_f < 1$ or $(1 - k\bar{r})/[1 - 2k\bar{r}\bar{h} - 2k \text{cov}(r, h)] < 1$ can be simplified as

$$\bar{r}(2\bar{h} - 1) + 2 \text{cov}(r, h) < 0.$$

If r and h are independent, *i.e.*, $\text{cov}(r, h) = 0$, the inequality holds when $\bar{h} < 1/2$, or HALDANE's rule follows when the average degree of dominance is smaller than one half.

Why should the sex-linked deleterious incompatible alleles be recessive, on average? A simple explanation is the "loss-of-function" theory spelled out in MULLER's model (discussed above). Indeed, some hybrid sterility and inviability genes behave as loss-of-function mutations (ORR 1992, 1993b). Another explanation is the theory of CHARLESWORTH *et al.* (1987). This theory shows that recessive or partially recessive advantageous mutations accumulate more rapidly when they are sex linked. If a significant proportion of substitutions accumulated on sex chromosomes are recessive or partially recessive, the recessive nature of the X-linked hybrid sterility and inviability genes is expected.

Experimental data: All the available experimental data on hybrid sterility and inviability are consistent with MULLER's recessivity model. First, it predicts that the major incompatible interactions causing hybrid sterility and inviability is between the X chromosome and the autosomes. Other types of interactions, such as Y-autosome and X-Y interactions are also expected on this hypothesis. Among the well-established incompatible interactions between heterospecific chromosomes, the most common form of interaction is, indeed, the X-

autosome interaction, which has been observed in species pairs *Drosophila pseudoobscura*/*D. persimilis* (DOBZHANSKY 1936), *D. pseudoobscura pseudoobscura*/*D. p. bogotana* (PRAKASH 1972), *D. hydei*/*D. neohydei* (SCHÄFER 1978), *D. virilis*/*D. lummei* (HEIKKINEN and LUMME 1991) and *D. simulans*/*D. sechellia* (ZENG and SINGH 1993). In the species pair *D. hydei*/*D. neohydei* (SCHÄFER 1978), interactions between different autosomes and between the *Y* chromosome and autosomes have also been found. Interactions between *Y* chromosome and autosomes have been observed in species pair *D. virilis*/*D. lummei* as well (HEIKKINEN and LUMME 1991). A well-established case of interactions between autosomes and *Y* chromosome is in the species pair *D. mojavensis* and *D. arizonensis* (VIGNEAULT and ZOUROS 1986; ZOUROS *et al.* 1988; PANTAZIDIS *et al.* 1993). Interactions between heterospecific sex chromosomes have been reported (CURTIS *et al.* 1980; COYNE 1985; ORR 1987) in cases of hybrid sterility in *Drosophila* and *Glossina*.

Another prediction of MULLER's recessivity model is that the incompatible genes, *i.e.*, hybrid sterility and inviability genes, are often recessive. Although there are very few well-described incompatible genes, the available data do show a recessive nature of hybrid sterility and inviability genes. The well-studied *SMF* (sperm motility factor) (VIGNEAULT and ZOUROS 1986; PANTAZIDIS *et al.* 1993) is recessive, homozygosity of *SMF* is required to cause sperm immotility. The *hms* gene on the fourth chromosome of *D. simulans* (it causes male sterility when introduced to the background of *D. melanogaster*) is completely recessive (ORR 1992). Another example is the study of SCHÄFER (1978), in which the recessive nature of the autosomal incompatibility genes is obvious. The autosomes involved in X-autosome, autosome-autosome and Y-autosome interactions have to be homozygous to produce sterility effects. The deleterious interacting genes involved in hybrid female sterility between *D. simulans* and *D. mauritiana* (or *D. sechellia*) are also completely recessive (L-W. ZENG and R. S. SINGH, unpublished data; DAVIS *et al.* 1994). Both *D. simulans* X-linked gene(s) and the *D. mauritiana* (or *D. sechellia*) autosomal genes have to be made homozygous to result in sterility. As sex-linked hybrid male sterility and inviability genes are in hemizygous condition, it is very difficult to demonstrate their recessivity. By artificially putting two different alleles on the same X chromosome, HUTTER *et al.* (1990) showed the recessive nature of the *hmr* genes on *D. melanogaster* X chromosome, which rescues inviable hybrid males produced from crossing *D. melanogaster* females to *D. simulans* males.

In summary, MULLER's recessivity model provides the simplest explanation of HALDANE's rule. It has also survived two experimental tests and two mathematical examinations and is consistent with virtually all experimental data. It remains a plausible explanation of HALDANE's rule.

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