Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

H. J. Muller and the “Competition Hoax”

James F. Crow¹

Laboratory of Genetics, University of Wisconsin, Madison, Wisconsin 53706

How much is evolution accelerated by sexual reproduction? (15 min.) MULLER (1958b)

HERMAN Joseph Muller—Joe, as he preferred to be called in his later life—is best known for his discovery of X-ray mutagenesis (Figure 1). Important as this is, it is but a tiny fraction of his work. In his introduction to Muller’s collected papers (MULLER 1962, p. v), Joshua Lederberg wrote: “It is not easy to find an original thought in biological theory that has not, in some way, been anticipated here—whether the topic be the ultramicroscopic gene, the fate of mankind on earth, or the cosmic origins of life. . . . Thoughtful reader—you will find a world of rediscovery here.” Muller’s breadth of interest was exemplified in his evolution course, which dealt with the origin of the universe and the earth, the beginnings of life, biological evolution (of course), and, finally, social evolution. His student Elof Carlson has written extensively about Muller’s life, both scientific and personal (CARLSON 1981, 2004).

Evelyn WITKIN (2000, p. 461) has discussed Muller’s pioneering work: “. . . throughout the ’20s and ’30s one geneticist, Hermann J. Muller, thought more deeply, wrote more extensively, and spoke more passionately about the nature of the gene than anyone else. Indeed, Muller laid the conceptual foundation of molecular biology to an extent that is not generally recognized.” His ideas on evolution are less well known, but in my view he belongs with the other great theorists (CROW 2005). Muller has been well represented in the pages of *GENETICS*. Since 1950 his name has appeared in the title or abstract of 46 articles. Here is a sample of articles that deal directly with his life and work: PAUL (1988), LEDERBERG (1991), CROW (1995), ZENG (1996), CROW and ABRAHAMSON (1997), TURELLI and ORR (2000), WAGNER and CROW (2001), and JOHNSON (2002).

Muller was one of the first to offer an explanation of why sexual reproduction is so ubiquitous. Along with

R. A. FISHER (1930), MULLER (1932) argued that a major advantage of sexual reproduction is that, by recombination, favorable mutations that occur in different individuals can be combined into the same lineage. Otherwise they can only compete with each other until one wins out. In two subsequent articles, MULLER (1958a, 1964) developed the theory quantitatively.

THE MULLER ARGUMENT

In an asexual strain, if two mutations are to be incorporated into the population, the second must occur in a descendant of the individual in which the first occurred. After the first mutation, the second will occur only after the population has attained a size such that the cumulative number of individuals is roughly the reciprocal of the mutation rate. The number of generations required will be designated by g . During this time a total number of mutations in the population will be Nug , where N is the population number and U is the mutation rate per individual, counting favorable mutations at all loci. In an asexual population, one mutation will be incorporated every g generations. In a sexual population, all the favorable mutations that occur during this period are potentially incorporated. Thus, roughly, the ratio of mutation incorporation in sexual and asexual populations is $Nug:1$. Of course, not all mutations will be successful, but if any substantial fraction of them are incorporated, there can be an enormous advantage to sexual reproduction, as Muller emphasized.

In his calculations, Muller assumed that the mutations would continue to increase exponentially at a rate determined by their effects on fitness, but he realized that there would be a slowing down as the mutant frequency increased. Motoo Kimura and I worked out the consequences of this decelerating effect, assuming a logistic growth curve (CROW and KIMURA 1965). Letting s be the selective advantage of a mutant allele, the

¹Address for correspondence: 445 Henry Mall, University of Wisconsin, Madison, WI 53706. E-mail: jfcrow@wisc.edu

FIGURE 1.—H. J. Muller and the X-ray machine with which he did his Nobel Prize-winning experiments at the University of Texas.

formula for R , the ratio of the allelic substitution rate in a sexual to that in an asexual population, is given by

$$R = (NU/s) \ln[N(e^{s/UN} - 1) + 1].$$

This analysis implied that the advantage of sexual reproduction would be greatest with a high mutation rate, large population, and individually small effects.

One aspect of this—that the advantage of sex is greatest for small s —did not make sense, since in the limit as $s \rightarrow 0$, there is obviously no advantage. It turned out, as first noted by MAYNARD SMITH (1971), that what was wrong in our formulation was not taking stochastic considerations into account. Thinking that early stochastic losses would affect sexuals and asexuals equally, we had naively assumed that each mutation could be treated deterministically.

The confusion was laid to rest by FELSENSTEIN (1974), who finally produced the definitive treatment through simulation studies. At the same time, he suggested a simple modification, which assumes that after the mutant frequency is large enough to escape stochastic loss, the increase follows the logistic pattern that we have assumed. This yields the approximation

$$R = 2NU \ln[2Ns(e^{1/2NU} - 1) + 1].$$

(Ironically, Felsenstein used Kimura's equations in his calculations.) This solved the major dilemma that had

bothered Kimura and me; the advantage of sexual reproduction now *increased* with s , although weakly. Finally, to my great relief, everything made sense. Furthermore, the relative rate of evolution in sexual *vs.* asexual strains became much more modest, with values in the range 1–10 rather than the thousands or more given by the earlier calculations.

GENE INTERACTION

It is sometimes said that the advantage of sex is that it provides a way to incorporate two mutations, one or both of which are individually deleterious, but beneficial in combination. Muller understood this point. In his characteristically convoluted, but always clear prose, MULLER (1964, p. 7) wrote:

What now about those genes whose advantage is negative, zero, or too minute for effective selection in the general population but which, when in combination with one or more other mutant genes of some particular kind, are advantageous enough to increase by differential multiplication? It is a widespread fallacy to suppose that sexual reproduction, through the recombination to which it gives rise, increases the likelihood of concatenation, within the same genotype, between an ordinarily non-advantageous gene, b , and another gene, a , in the company of which b would be advantageous, and that in this way recombination speeds evolutionary change.

Muller goes on to argue that each mutant must be individually advantageous if the combination is to prevail. If deleterious, they can hardly ever reach frequencies high enough for potential mates to find each other.

Kimura and I discussed the conditions under which collectively beneficial combinations of individually deleterious genes can evolve. Something special is required, such as a subdivided population, assortative mating, tight linkage, or interspersed asexual generations. "In general, sexual reproduction can be a distinct disadvantage if evolution progresses mainly by putting together groups of individually deleterious, but collectively beneficial mutations. It seems to us that if this type of gene action were the limiting factor in evolution at the time sexual reproduction first evolved, sexual recombination might never have been 'invented'" (Crow and KIMURA 1965, p. 445). Nevertheless, with digital organisms LENSKI *et al.* (2003) have shown that such combinations can indeed sometimes occur in asexual systems.

MULLER'S RATCHET

Although not related to adaptive evolution, Muller, in his 1964 article, tossed out in a single sentence an idea that has later had an enormous influence: "If we disregard advantageous mutations ... we find that an asexual population incorporates a kind of ratchet mechanism, such that it can never get to contain, in any of its lines, a load of mutations smaller than that

FIGURE 2.—A postcard from Muller discussing the “competition hoax.” It was his custom to send postcards loaded with almost indecipherable hieroglyphics. The card was addressed to me while I was visiting at Stanford University.

already existing in its at present least-loaded lines” (p. 8). If each individual had at least one deleterious mutant gene, in the absence of recombination the population could never have less than this number, except by highly improbable back mutation. In contrast, by recombination a mutant-free individual could easily arise. Muller’s simple idea, first emphasized by FELSENSTEIN (1974), has since become one of the major arguments for the value of sexual reproduction. It has generated a flood of articles emphasizing quantitative aspects, for example, HAIGH (1978), KONDRASHOV (1994), and GORDO *et al.* (2002).

Muller is also largely responsible for another idea regarding deleterious mutations. In discussing the mutation load (MULLER 1950), he pointed out that the load can be reduced if several mutant alleles can be picked off in one genetic death. He did not think that actual levels of epistasis were sufficient for this to make much difference. It was realized, however, that truncation (rank-order) selection can mimic a high level of epistasis by eliminating all individuals with more than a threshold number of mutations, but this did not seem realistic for natural populations. CROW and KIMURA (1978), however, showed that a crude approximation to rank-order selection is almost as effective. This could be a good model for density-regulated populations. KONDRASHOV (1984) used this result to develop the “deterministic mutation hypothesis,” which states that a major advantage of sexual reproduction is efficiency of elimination of deleterious mutations.

THE COMPETITION EFFECT (CLONAL INTERFERENCE)

In discussing the advantages of sexual reproduction, MULLER (1958a, p. 151) wrote: “There is one factor that tends to make the situation even worse than this for the asexual as compared with the sexual population. This lies in the fact that in the former the favorable lines

usually enter into an increasingly restrictive competition with one another, thus reducing each other’s selective advantage, whereas in the latter the formation of combinations of them tends increasingly to substitute cooperation for competition.”

It is indeed true that, when multiple favorable mutants arise, they compete with each other, each slowing the rate at which the others can increase. But it seemed to Kimura and me that this is not restricted to an asexual population. Individuals compete for survival irrespective of their mode of reproduction. In sexual species, there is additional competition for mates.

I discussed this question with Muller several times. An example that makes the situation clear is to assume an infinitely large haploid species with two loci each with two alleles segregating in the population. The four haploid genotypes AB, Ab, aB, and ab have relative fitnesses x_1 , x_2 , y_1 , and 1 and, at linkage equilibrium, the frequencies are px , $p(1-r)$, $(1-p)y$, and $(1-p)(1-r)$. Such a population evolves at exactly the same rate with or without recombination. Hence any competition effect must be the same in both populations. Muller accepted this and other arguments. Figure 2 shows a postcard from him disavowing what he called the “competition hoax.”

Dear Jim: You’re so right! But first, after reading your exposé of the competition hoax, I had the half-baked thought that the mutual restraint exerted by advantageous mutants on the other’s increase in asexual forms would delay the time when an additional advantageous mutant would arise in an advantaged line of descent. Then I realized that (it) wouldn’t matter, since in that case the additional mutant would arise anyway in one of the alternative advantaged lines instead of the “propositus” line. I’m so glad you found this error before sending the article for publication, as I shouldn’t have wanted to carry a double tail between my legs, one’s enough. Tell Kimura when you write him next that I much appreciated his colored postcard (acknowledging my reprints) and apologize mightily for having misled him (and you) in this way. As ever, Joe.

There is no implication that competition is necessarily the same in sexual and asexual species. Competition depends on the frequency and fitness of the genotypes in a population at any particular time, and since the allele-frequency trajectories in sexual and asexual species may be different, so may the competition effect. The effect may indeed be greater in sexual species if there is additional competition for mates. And of course stochastic processes intrude.

Muller said that he would like to write an article about this subject, so Kimura and I omitted any mention of the competition effect in our 1965 article. Alas, Muller's death came before he had a chance to do the promised writing. We alluded to this briefly in a later article (CROW and KIMURA 1969), but it has not had much notice.

The competition effect (now called clonal interference) has since been explored extensively. GERRISH and LENSKI (1998) did a particularly incisive study. They showed in mathematical detail the effect of clonal interference on fixation probabilities, expected substitution rate, and rate of fitness increase. MIRALLES *et al.* (1999) have applied the theory to RNA viruses and ROZEN *et al.* (2002) to *Escherichia coli*.

FISHER (1930, p. 122) noted that a new favorable mutation in an asexual species has a very uncertain fate. In addition to the usual stochastic loss, whether the mutation prevails depends on other genotypes in the population, including its own residual genotype. A beneficial mutation may fail if a still-better one occurs or already exists. A similar situation has been studied in detail, both mathematically and experimentally, by HEGRENESS *et al.* (2006). Despite the complications of multiple mutations and clonal interference, these authors found a remarkable simplification: an "equivalence principle" whereby all beneficial mutations confer approximately the same fitness advantage. The generality of this simple approximation is the subject of future research.

KIM and ORR (2005) have done a combined mathematical and simulation study of evolution in sexual and asexual populations. They find, in some circumstances at least, that clonal interference has little effect, *e.g.*, on transition probabilities from the wild-type to various beneficial mutations. They also emphasize that different results can emerge when beneficial mutations have quite different fitnesses. Clearly, there are interesting complexities yet to be discovered.

To conclude, the competition effect is not a hoax; indeed, it is very real. However, it need not be restricted to clonal populations.

Rich Lenski, Allen Orr, and Bret Payseur read the manuscript and made suggestions that materially improved it.

LITERATURE CITED

- CARLSON, E. A., 1981 *Genes, Radiation, and Society: The Life and Work of H. J. Muller*. Cornell University Press, Ithaca, NY.
- CARLSON, E. A., 2004 *Mendel's Legacy: The Origin of Classical Genetics*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- CROW, J. F., 1995 Quarreling geneticists and a diplomat. *Genetics* **140**: 421–426.
- CROW, J. F., 2005 Herman Joseph Muller, evolutionist. *Nat. Rev. Genet.* **6**: 941–945.
- CROW, J. F., and S. ABRAHAMSON, 1997 Seventy years ago: mutation becomes experimental. *Genetics* **147**: 1491–1496.
- CROW, J. F., and M. KIMURA, 1965 Evolution in sexual and asexual populations. *Am. Nat.* **99**: 439–450.
- CROW, J. F., and M. KIMURA, 1969 Evolution in sexual and asexual populations. A reply. *Am. Nat.* **103**: 89–91.
- CROW, J. F., and M. KIMURA, 1978 Efficiency of truncation selection. *Proc. Natl. Acad. Sci. USA* **76**: 396–399.
- FELSENSTEIN, J., 1974 The evolutionary advantage of recombination. *Genetics* **78**: 737–756.
- FISHER, R. A., 1930 *The Genetical Theory of Natural Selection*. The Clarendon Press, Oxford.
- GERRISH, P. J., and R. E. LENSKI, 1998 The fate of competing beneficial mutations in an asexual population. *Genetica* **102/103**: 127–144.
- GORDO, I., A. NAVARRO and B. CHARLESWORTH, 2002 Muller's ratchet and the pattern of variation at a neutral locus. *Genetics* **161**: 835–848.
- HAIGH, J., 1978 The accumulation of deleterious genes in a population: Muller's ratchet. *Theor. Popul. Biol.* **14**: 251–267.
- HEGRENESS, M., N. SHORESH, D. HARTL and R. KISHONY, 2006 An equivalence principle for the incorporation of favorable mutations in asexual populations. *Science* **311**: 1615–1617.
- JOHNSON, N. A., 2002 Sixty years after "Isolating Mechanisms, Evolution and Temperature": Muller's legacy. *Genetics* **161**: 939–944.
- KONDRASHOV, A., 1984 Deleterious mutations as an evolutionary factor. I. The advantage of recombination. *Genet. Res.* **44**: 199–217.
- KONDRASHOV, A. S., 1994 Muller's ratchet under epistatic selection. *Genetics* **136**: 1469–1473.
- LEDERBERG, J., 1991 The gene (H. J. Muller 1947). *Genetics* **129**: 313–316.
- LENSKI, R. E., C. OFRIA, R. T. PENNOCK and C. ADAMI, 2003 The evolutionary origin of complex features. *Nature* **423**: 139–144.
- KIM, Y., and H. A. ORR, 2005 Adaptation in sexuals *vs.* asexuals: clonal interference and the Fisher-Muller model. *Genetics* **171**: 1377–1386.
- MAYNARD SMITH, J., 1971 What use is sex? *J. Theor. Biol.* **30**: 319–335.
- MIRALLES, R., P. J. GERRISH, A. MOYA and S. F. ELENA, 1999 Clonal interference and the evolution of RNA viruses. *Science* **285**: 1745–1747.
- MULLER, H. J., 1932 Some genetic aspects of sex. *Am. Nat.* **66**: 118–138.
- MULLER, H. J., 1950 Our load of mutations. *Am. J. Hum. Genet.* **2**: 111–176.
- MULLER, H. J., 1958a Evolution by mutation. *Bull. Am. Math. Soc.* **64**: 137–160.
- MULLER, H. J., 1958b How much is evolution accelerated by sexual reproduction? *Anat. Rec.* **132**: 480–481.
- MULLER, H. J., 1962 *Studies in Genetics: The Selected Papers of H. J. Muller*. Indiana University Press, Bloomington, IN.
- MULLER, H. J., 1964 The relation of recombination to mutational advance. *Mutat. Res.* **1**: 2–9.
- PAUL, D., 1988 H. J. Muller, communism and the cold war. *Genetics* **119**: 223–225.
- ROZEN, D. E., J. A. G. M. DE VISSER and P. J. GERRISH, 2002 Fitness effects of fixed beneficial mutations in microbial populations. *Curr. Biol.* **12**: 1040–1045.
- TURELLI, M., and H. A. ORR, 2000 Dominance, epistasis and the genetics of postzygotic isolation. *Genetics* **154**: 1663–1679.
- WAGNER, R. P., and J. F. CROW, 2001 The other fly room: J. T. Patterson and Texas genetics. *Genetics* **157**: 1–5.
- WITKIN, E. M., 2000 H. J. Muller and the nature of the gene. *Genetics* **157**: 461–469.
- ZENG, L. W., 1996 Resurrecting Muller's theory of Haldane's rule. *Genetics* **143**: 603–607.