

Genetic Hitchhiking and the Evolution of Reduced Genetic Activity of the Y Sex Chromosome

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ABSTRACT

A new model for the evolution of reduced genetic activity of the Y sex chromosome is described. The model is based on the process of genetic hitchhiking. It is shown that the Y chromosome can gradually lose its genetic activity due to the fixation of deleterious mutations that are linked with other beneficial genes. Fixation of deleterious Y-linked mutations generates locus-specific selection for dosage tolerance and/or compensation. The hitchhiking effect is most pronounced when operating in combination with an alternative model, Muller's ratchet. It is shown, however, that the genetic hitchhiking mechanism can operate under conditions where Muller's ratchet is ineffective.

A remarkable feature of sex chromosomes in many different taxa is the disparity in genetic information found on the two homologous types. The Y chromosome (W chromosome in a WZ system) carries much less genetic information than the X chromosome. Comparative reviews of sex chromosomes indicate that the X and Y chromosomes evolved from a pair of fully homologous autosomes (MITTWOCH 1967; OHNO 1967; WHITE 1973; BULL 1983).

Over the past 75 yr several models have been proposed to explain the breakdown in genetic activity of the Y chromosome (MULLER 1918; FISHER 1935; HAMILTON 1967; NEI 1970; LUCCHESI 1978; CHARLESWORTH 1978). CHARLESWORTH (1978) criticized all previous models, and concluded that only the operation of Muller's ratchet (FELSENSTEIN 1974; HAIGH 1978) (see below) is a general mechanism for the evolution of a degenerate Y chromosome. Here I suggest the operation of a second process, genetic hitchhiking (MAYNARD SMITH and HAIGH 1974), to account for the breakdown in Y chromosome activity. The hitchhiking mechanism can operate in combination with Muller's ratchet, but it can also operate in circumstances where the ratchet model is ineffective.

The ratchet model has two important limitations, both of which were clearly articulated by CHARLESWORTH (1978). First, the ratchet model "requires that inactivation of the Y chromosome and enhancement of the X chromosome in males must be nonspecific with respect to which loci are affected. This is because the selective advantage of both of these phenomena [Y inactivation and dosage compensation] is due to the fact that the Y chromosome of each individual carries a number of mutant genes, but the actual loci involved vary from individual to individual" (CHARLESWORTH 1978) (bracketed portions inserted for clarity).

Second, in order for the ratchet model to operate,

the chromosome-wide mutation rate must be large compared to the selective disadvantage of individual mutants. More specifically, $N_m e^{-U/s^*} < 1000$ for the ratchet mechanism to operate at a rate that would likely have any biological significance, and $N_m e^{-U/s^*} \leq 100$ for the ratchet mechanism to proceed at an appreciable rate, where U is the Y chromosome-wide mutation rate, N_m is the effective number of males in the population, and s^* is the decrement to fitness imparted to an individual carrying a single Y-linked deleterious mutation in the heterozygous state [adapted from MAYNARD SMITH (1978) p. 34].

Evaluation of the above inequalities is impeded by our ignorance of the parameter values of N_m , U , and s^* in natural populations. To evaluate the above inequalities CHARLESWORTH (1978) used *Drosophila melanogaster* as a model system. Using data summarized in SIMMONS and CROW (1977) he argued that the maximum mean value of s^* is 0.007 [for mildly deleterious mutations in the heterozygous state, see SIMMONS and CROW (1977) p. 54 for definition] and that 0.055 would have been a minimum chromosome-wide mutation rate of the ancestral Y chromosome. Using these values, both of MAYNARD SMITH's inequalities are met, and stimulation work by HAIGH (1978) indicates that deleterious mutations would slowly accumulate on the Y chromosome. The long-term accumulation of such mildly deleterious mutations could ultimately lead to the evolution of an inert Y chromosome, as described in CHARLESWORTH (1978).

The value of s^* used by CHARLESWORTH, however, only represents the viability component of the mutations' affect on fitness. Data surveyed by SIMMONS and CROW (1977) indicate that when fertility and mating success are included, the mean value of s^* may be closer to 0.02, irrespective of the impact of the mutations when homozygous. CHARLESWORTH noted this

problem but did not investigate the consequences. Later work by SIMMONS, PRESTON and ENGELS (1980) supported the conclusion that the mean value of s^* is about 0.02 for newly arising mutations, but also suggested that many of the viability mutations that accumulate in population cages may pleiotropically enhance other fitness components. The appropriate value of s^* is important because the operation of Muller's ratchet is highly sensitive to this parameter. If the detrimental affect of most mildly deleterious mutations, in the heterozygous condition, is closer to 0.02 than to 0.007, then neither of MAYNARD SMITH's inequalities would be met and Muller's ratchet would operate at a negligible rate in the *D. melanogaster* model system evaluated by CHARLESWORTH (1978). In any case, since empirical estimates of the mean value of s^* are so imprecise, the question, of whether or not the *D. melanogaster* data support the operation of Muller's ratchet, is moot.

These arguments in no way invalidate the ratchet model as a potential mechanism causing the *Y* chromosome to degenerate. They do point out, however, the sensitivity of the Muller's ratchet model to parameter values for which we are uncertain. Here I present an alternative mechanism for the breakdown in genetic activity of the *Y* chromosome that can work in conjunction with Muller's ratchet, and also can operate when the ratchet mechanism cannot.

THE GENETIC HITCHHIKING MODEL

Preliminary concepts: The assumptions and initial conditions for the hitchhiking model are identical to those for the ratchet model. We start with a finite population in which all or part (the differential segment) of the *Y* chromosome has recently stopped recombining with the *X* [see BULL (1983) and RICE (1987) for a review of why recombination between *X* and *Y* may breakdown]. Three processes will impinge on the *Y* chromosome: selection, mutation and sampling error. Because the *Y* chromosome is permanently heterozygous, and because it fails to recombine with the *X*, selection acts at the level of the entire *Y* chromosome.

Let u be the mutation rate per locus, and U be the mutation rate per *Y* chromosome ($U = ju$; where j is the number of loci on the *Y* chromosome or its differential segment). In what follows we will focus on mutations of the mildly deleterious type, producing a reduction in fitness of $<3\%$ when heterozygous. Data surveyed by SIMMONS and CROW (1977) and SIMMONS, PRESTON and ENGELS (1980) indicate that most detrimental mutations of *D. melanogaster* would fall into this category. Other more harmful mutations may be produced, but these will rapidly be eliminated by natural selection and are not considered here.

Recall that the selective disadvantage of a mutation expressed in the heterozygous state is denoted by s^* .

The actual selective disadvantage (s) of a *Y*-linked mutation will be, $s = s^*(1 - q) + s'q$, where q is the frequency of the deleterious mutation on the *X* chromosome and s' is the selective disadvantage of the mutation when homozygous. As pointed out by FISHER (1935) this means that even fully recessive harmful *Y*-linked mutations are selected against. We will assume, as did HAIGH (1978) and CHARLESWORTH (1978), that the detrimental effects of deleterious mutations combine multiplicatively, so that the fitness of an individual carrying k deleterious mutants is $(1 - s)^k$.

Adapting equations 1-7 of HAIGH (1978) to the case of a nonrecombining and permanently heterozygous *Y* chromosome, a deterministic equilibrium distribution of *Y* chromosomes carrying different numbers of mutations can be determined. This equilibrium distribution represents the balance between chromosome-wide mutation and selection rates. The expected size of the chromosome class with the smallest number of mutations is $N_0 = N_m e^{-U/s}$ (HAIGH 1978).

Whenever $N_0 < 1000$, sampling error will eliminate the class of *Y* chromosomes carrying the fewest mutations faster than backward-mutation can regenerate them, and the *Y* chromosome will continuously accumulate deleterious mutations (MAYNARD SMITH 1978, p. 34). The smaller the value of N_0 the faster the accumulation of detrimental genes on the *Y* chromosome.

The accumulation of deleterious mutations, due to sampling error in an asexual genome, was termed "Muller's ratchet" by FELSENSTEIN (1974). CHARLESWORTH applied this process to the case of a nonrecombining *Y* chromosome, which represents an asexual component in an otherwise sexual genome. CHARLESWORTH (1978) proposed that the continuous erosion in the quality of the *Y* chromosome via Muller's ratchet would select for: (1) a nonspecific and chromosome-wide (or block-wide, see below) reduction in the activity of the *Y* chromosome, and (2) a nonspecific and chromosome-wide (or block-wide) increase in the activity of the *X* chromosome to partially eliminate (dilute) the deleterious effects of mutant *Y*-linked genes. Both responses must be nonspecific with respect to which sex chromosome loci are affected because, according to CHARLESWORTH (1978), Muller's ratchet is not expected to produce a high frequency of mutations at any single locus. Ultimately these changes in *X* and *Y* chromosome activity, in combination with the evolution of dosage compensation, could result in virtually complete breakdown in the genetic activity of the *Y* chromosome [see CHARLESWORTH (1978) for details].

Genetic hitchhiking when Muller's ratchet does not operate: When the ratio U/s is small, neither of MAYNARD SMITH's inequalities will be met and Muller's ratchet is not expected to be effective. Even when

Muller's ratchet does not turn, however, mutation pressure is expected to produce a distribution of *Y* chromosomes that differ in the number of mutations that they carry. Adapting equation (6) of HAIGH (1978) to the case of a nonrecombining *Y* chromosome, the deterministic equilibrium proportion (P) of *Y* chromosomes carrying k mutations is, $P_k = e^{U/s(U/s)^k/k!}$.

Suppose that a *Y* chromosome (or its differential segment) has recently stopped recombining with the *X*. Mutation and selection pressure will generate a distribution of *Y* chromosomes carrying different numbers of mutations. The deleterious alleles that accumulate on the *Y* chromosome would be expected to be dispersed among all of the nonrecombining loci, with a low expected frequency of deleterious alleles at any specific locus (HAIGH 1978; CHARLESWORTH 1978).

Next suppose that a change in the environment, or some other factor, causes selection to change, so that a new allele becomes favored at a sex chromosome locus. In a finite but large population, this newly favored allele would be expected to be present on the *Y* chromosome at low frequency due to mutation selection balance. In all but an extremely large population, the number of copies of the beneficial allele will be quite small, and only one of these will be present in the most favorable genetic background. Because P_0 generally will be a small fraction of the total *Y* chromosome distribution, the new beneficial allele in the best genetic background will rarely occur against a background of the fewest number of mutations. If the new beneficial allele is absent in the population of *Y* chromosomes, it will recurrently be introduced by mutation.

Whenever the chromosome carrying the new beneficial allele in the best genetic background has a net selective advantage relative to those *Y* chromosomes carrying the fewest mutations, it can rapidly accumulate in the population. The accumulation can be rapid because selection on *Y* chromosomes is equivalent to selection in a haploid population.

The time (in generations, G) to fixation is approximately, $G = [(2/s^{**})\ln(N_m - 1)] + 1$ [adapted from CROW and KIMURA (1970), p. 193], where s^{**} is the net selective advantage of the *Y* chromosome carrying the new beneficial allele in the fittest genetic background. For example, when $N_m = 50,000$ and $s^{**} = 0.05$, only 434 generations are required for the fixation of the chromosome that carries the new beneficial allele. ENDLER (1986, Ch. 7) provides empirical evidence that values of s^{**} exceeding 0.05 are not uncommon in nature, but this conclusion is controversial.

The above demonstrates how progressive selection at a sex-linked locus can rapidly cause the fixation of a single *Y* chromosome in finite populations. There

are two consequences of this rapid fixation process. First, it can cause the class of *Y* chromosome carrying the fewest mutations to be eliminated and replaced with a more heavily mutated chromosome that also carries the beneficial allele. This has the same net effect as Muller's ratchet except that **selection replaces sampling error as the process increasing the number mutations found on the least mutated *Y* chromosome.**

Second, the rapid fixation of a single *Y* chromosome purges the diversity of accumulated mutations from the pool of *Y* chromosomes. This focuses the mutational load from a dispersed state, spread out over all loci, to a highly concentrated state, by producing fixation of mildly deleterious mutations at a relatively small number of loci. **Thus genetic hitchhiking can lead to the accumulation and fixation of *Y* linked mutations.**

Once mutations are fixed on the *Y* chromosome, there will be natural selection for wild-type alleles at these loci. Because: (1) new beneficial alleles are rare, (2) sampling error eliminates most beneficial mutations before they can begin to accumulate in finite populations, and (3) many beneficial mutations will be "trapped" in an inferior genetic background due to lack of recombination between *X* and *Y* chromosomes; thousands of generations are expected to pass before mutation and selection can eliminate fixed *Y* linked mutations in all but extremely large populations [see CROW and KIMURA (1970), Section 8.8 for discussion]. During the intervening period, other evolutionary events may preempt the reestablishment of wild-type alleles on the *Y* chromosome.

Null alleles initially fixed on the *Y* chromosome: Once a group of mildly deleterious mutations is fixed due to genetic hitchhiking, all males within the population will have only a single copy of the wild-type allele (A_1 ; including all allelomorphs with unit relative fitness) at the affected loci. Some of these mutant alleles may be null alleles (A_0), but most probably will be functional (e.g., VOELKER *et al.* 1980). In the case of null alleles, males (A_0A_1) will produce only half as much gene product as females (A_1A_1), and dosage imbalance will result in males but not females [see for example BAVERSTOCK *et al.* (1982)]. This will produce natural selection for both dosage compensation and/or "dosage tolerance." By dosage tolerance I mean the capacity of the two sexes to accommodate different concentrations of gene product. The first step in the evolution of dosage compensation and/or dosage tolerance may be the evolution of enhanced production by X-linked genes.

Consider a regulatory mutation (A_e) of an X-linked allele that produces an excess of gene product compared to the wild-type allele. Such an allele will increase the concentration of gene product in both sexes. The proportionate affect in males will be greater when A_e is rare, however, since males carry

only a single functional gene copy when the *Y* chromosome is fixed for a null allele. For example, suppose A_e increased production by 25%. Initially the allele will be rare in the population and virtually all females carrying the allele will be heterozygous while all males will be hemizygous. Males carrying A_e will produce 25% more gene product while females will produce only 12.5% more. Thus A_e alleles, when rare, partially correct dosage imbalance in males by a larger degree than they disrupt dosage balance in females. Elsewhere (RICE 1984) I have shown that such an A_e allele would increase to high frequency despite its detrimental affect to females, even when the homozygous fitness cost to females exceeds the gain to males.

The above demonstrates that once a null allele becomes fixed on the *Y* chromosome, due to genetic hitchhiking, A_e alleles can invade on the *X* chromosome. The accumulation of such alleles reduces the dosage imbalance of males but also creates a new dosage imbalance in females. If genetic variability for enhanced output of *X*-linked genes is available, then the sexual asymmetry in the expression of A_e alleles will cause the evolution of enhanced *X* output at individual loci despite the reduction in fitness to females (RICE 1984). The evolution of increased output by *X*-linked genes would reduce the degree of dosage imbalance experienced by males.

Thus asymmetrical selection pressure can reduce dosage imbalance in males, but not eliminate it. Once an equilibrium dosage evolves, there will be continued natural selection for both dosage tolerance and dosage compensation. There is now substantial evidence in birds that dosage compensation has never evolved, at least not on a chromosome-wide basis as has been observed in mammals and *Drosophila* [see for example OHNO (1967) and BAVERSTOCK *et al.* (1982)]. In birds it appears that males (ZZ) produce approximately twice as much gene product as females (ZW) at *Z*-linked loci.

The fact that birds experience dosage imbalance at many loci simultaneously, suggests that they have evolved dosage tolerance, since hemizygosity for major portions of a nondosage compensated chromosome is generally lethal (*e.g.*, Lindsley *et al.* 1972). This is not to say that birds do not pay some "physiological price" for lack of dosage compensation. At the very least, the excess gene product produced in females must have some cost due to wasted resources. As will be shown below, the evolution of dosage tolerance is expected to evolve in a gradual fashion as an increasing number of null alleles accumulate on the *Y* chromosome.

Non-null mutations fixed on the *Y* chromosome: Many, if not most, of the mutations fixed on the *Y* chromosome will not be null alleles, but instead will be functional genes that produce inferior gene product. In this case there may still be selection for *X*-

linked genes that produce an excess of gene product.

Consider a *Y* chromosome locus coding for an enzyme and suppose the fixed mutant allele (A_d) produces a defective but physiologically active enzyme. In this case selection would favor a nonfunctional *Y*-linked allele as long as the fitness cost of dosage imbalance was small relative to the fitness gain associated with not expressing the mutant *Y*-linked allele. It may frequently happen, however, that the cost of dosage imbalance precludes this scenario. Null alleles on the *Y* chromosome may still become selectively favored, however, but only after the evolution of dosage tolerance.

To understand why, again assume genetic hitchhiking causes the fixation of a physiologically active but defective *Y*-linked enzyme. Next consider an *X*-linked regulatory mutation that produced excess normal enzyme. In males the higher concentration of normal enzyme could competitively displace the defective enzyme produced by the *Y*-linked locus. If the advantage to males of such an *X*-linked regulatory mutation exceeded the dosage cost to females (which will be smallest when A_d is rare), then enhanced *X* output could evolve, as well as dosage tolerance, by the process described above for *Y*-linked null alleles. Once dosage tolerance evolves, then a nonfunctional *Y*-linked gene would be selectively favored over an active *Y*-linked mutation, as long as $(1 - p) \times$ (the selective advantage of A_0 when heterozygous) $> (-p) \times$ (the selective disadvantage of A_0 when homozygous); where p is the frequency of A_0 on the *X* chromosome.

The continued accumulation of mutations on the *Y* chromosome: In order for the genetic hitchhiking mechanism to continually accumulate mildly deleterious mutations on the *Y* chromosome, recurrent episodes of progressive selection must occur for *Y*-linked genes. This is necessary to repeatedly cause the fixation of additional *Y*-linked mutations.

There are several reasons why an initial burst of progressive evolution may be expected after the *X* and *Y* stop recombining. First, breakdown in recombination between the *X* and *Y* chromosomes facilitates the evolution of *Y*-linked genes with sex-specific fitness effects. Theoretical work by FISHER (1931), CHARLESWORTH and CHARLESWORTH (1976, 1980), BULL (1983), and RICE (1986, 1987) demonstrates how *Y*-linkage can permit genes with sex specific fitness effects to accumulate, that could not do so if the *X* and *Y* chromosomes recombined. Many of these genes are expected to affect sexually selected characters, which are susceptible to runaway sexual selection (FISHER 1958). Because sexual selection can be quite intense in nature, selection coefficients for *Y*-linked beneficial mutations may be large, thereby facilitating the hitchhiking process.

A second factor, promoting a burst of progressive

evolution of the *Y* chromosome (segment) is the potential for *Y*-linked supergene formation. Theoretical work by CHARLESWORTH and CHARLESWORTH (1976, 1980) indicates that many gene combinations with epistatic fitness interactions can only accumulate when interlocus recombination rates are sufficiently small. Breakdown in recombination between the *X* and *Y* chromosomes (segments) can enable supergenes to evolve which were previously preempted by recombination.

A third mechanism, contributing to the burst of progressive evolution of the *Y* chromosome (segment), is the build up of natural selection for null alleles on the *Y* chromosome, as described above. This would be expected to accrue as dosage tolerance (and/or dosage compensation) evolves. As dosage tolerance (compensation) evolves for *X*-linked loci, due to the initial fixation of detrimental but functional alleles on the *Y* chromosome, there ultimately will be selection for nonfunctional alleles at the corresponding loci on the *Y* chromosome. Those *Y* chromosomes that contain one or more null alleles, against a genetic background that gives them a net selective advantage, will become selectively favored and will initiate an episode of *Y* chromosome replacement.

Genetic hitchhiking when Muller's ratchet does operate: Although the hitchhiking process can operate alone, it probably occurs most commonly in combination with Muller's ratchet. In this case, genetic hitchhiking will increase the rate at which the ratchet turns, and also produce fixation of *Y*-linked mutations on this chromosome. This fixation of *Y*-linked mutations will produce locus-specific selection for dosage tolerance/compensation, as described above.

When operating alone, hitchhiking will break down the activity of the *Y* chromosome (segment) at a rate that depends on the availability of *Y*-linked beneficial mutations. If most *Y*-linked beneficial mutations have only a small effect on fitness, then only a small number of deleterious mutations will "hitchhike" during each episode of progressive evolution, and the *Y* chromosome would break down much more slowly than when genetic hitchhiking is operating in combination with Muller's ratchet.

Interestingly, a special form of hitchhiking can operate in the absence of progressive evolution, when Muller's ratchet is operating. Consider a population with some arbitrary distribution of *Y*-linked mutations, and with in which the "best" *Y* chromosome contains >0 mutations. Each generation, on average, selection will increase the frequency of the chromosome class with the fewest mutations, and decrease the frequency of all more highly mutated chromosomal classes. Acting simultaneously, mutation pressure will convert some chromosomes from lower to more highly mutated classes. As a consequence of mutation and selection pressure, copies of chromosomes originating in

the best class will unidirectionally flux through the distribution as mutation pressure recurrently degrades them. In a finite population, mutation and selection pressure will ultimately cause all members of the most mutated chromosome class, and all intervening classes, to be derived from one of the best chromosomes. Thus eventually all chromosomes in the population will be derived from one member of the best class, and all (or virtually all) mutations originating on this founding chromosome will become fixed on the *Y* chromosome. In this case, a group of mutations "hitches a ride" to fixation (on the *Y* chromosome) by virtue of being initially associated with the most nonmutated genetic background.

DISCUSSION

The major advantage of the genetic hitchhiking model is that it can apply under conditions where the ratchet model can operate and when it cannot. Thus it both complements and extends the ratchet model. The ratchet model predicts that deleterious mutations will accumulate on the *Y* chromosome, but that these will be distributed in a diffuse pattern, *i.e.*, each individual locus is predicted to have a low frequency of mutant alleles (CHARLESWORTH 1978). The fact that individual loci are not expected to have a high concentration of mutant alleles, lead CHARLESWORTH (1978) to hypothesize that the reduced activity of the *Y* chromosome must occur on a chromosome-wide (or block-wide) basis, rather than on a locus by locus basis. For such a chromosome- or block-wide inactivation of the *Y* chromosome to evolve, some complementary mechanism must also evolve to prevent the lethal effects associated with making a large portion (*i.e.*, more than a few centimorgans) of the *X* chromosome simultaneously hemizygous (*e.g.*, LINDSLEY *et al.* 1972).

CHARLESWORTH (1978) suggested that the concomitant evolution of dosage compensation, that gradually evolves as deleterious mutants accumulate via Muller's ratchet, could make the transition possible. This form of dosage compensation, however, must act non-specifically with respect to which loci are compensated (*i.e.*, large blocks of genes must be simultaneously dosage compensated), since no single locus would be expected to have a high frequency of deleterious alleles (CHARLESWORTH 1978).

Data that have accumulated from *Drosophila* studies since the publication of CHARLESWORTH (1978) do not support the hypothesis of nonspecific block-wide dosage compensation [see for review BAKER and BELOTE (1983)]. For example, small segments of the *X* chromosome translocated to the autosomes retain their dosage compensation, while small segments of autosomes translocated to the *X* chromosome are uncompensated. These empirical observations, and others such as the lack of dosage compensation of the *X*-

linked yolk proteins (*YP*), support the conclusion that dosage compensation is highly localized, at least to the regional level of 2–3 loci (BAKER and BELOTE 1983).

Furthermore, the accumulating evidence in birds (Aves) and butterflies (Lepidoptera) that dosage compensation never evolved in these groups, argues against a requisite tight coupling between the evolution of dosage compensation and a degenerate *Y* chromosome. Thus in these taxa it seems unlikely that Muller's ratchet alone could have led to the evolution of a degenerate *Y* (*W*) chromosome, at least not via the dosage compensation scheme proposed by CHARLESWORTH [but see the alternative explanation of CHARLESWORTH (1978), p. 5620].

The hitchhiking model, however, does not require nonspecific inactivation of the *Y* chromosome nor dosage compensation of the *X* chromosome. Instead it predicts a locus by locus evolution of *Y* inactivation via the accumulation of null alleles and the concomitant evolution of dosage tolerance and/or dosage compensation.

The second problem with the ratchet model is that it is ineffective unless the *Y* chromosome (or its differential segment) is sufficiently large, *i.e.*, large enough for the chromosome- (segment-) wide mutation rate to exceed the critical value determined by $U > s(\ln[N_m] - 6.9)$; adapted from MAYNARD SMITH (1978). Since values for all of the parameters used in this calculation are empirically uncertain, we do not know the true domain of applicability for the Muller's ratchet model. Small differential segments, such as those found in the guppy (*Poecilia reticulata*) and the medaka (*Orizias latipes*), almost certainly could not have broken down via the ratchet mechanism, yet there is empirical evidence for their partial degradation (*e.g.*, WINGE and DITLEVSON 1947; YAMAMOTO 1969; HASKINS, YOUNG and HASKINS 1970; FARR 1981).

A recent study that supports the operation of the hitchhiking model is the cytological work of STEINEMANN (1982) with *Drosophila miranda*. In this species a *Y*-autosome Robertsonian-fusion has placed a large segment of formerly autosomal genes onto the *Y* chromosome. STEINEMANN used hybridization techniques to demonstrate that the neo-*Y* chromosome segment has been "invaded" by hundreds of moderately repetitive DNA sequences. No such invasion was found on the neo-*X* homolog. STEINEMANN suggested that these moderately repetitive sequences probably represent transposable elements that have been incorporated into the permanently heterozygous neo-*Y*, but not into the neo-*X* chromosome. Interestingly, these sequences are inserted throughout the neo-*Y* chromosome and are not found exclusively in those segments that are newly dosage compensated (STROBEL, PELLING and ARNHEIM 1978). CHARLESWORTH, LANGLEY and STEPHAN (1986) have shown that inactivation via trans-

posable elements may also be consistent with the Muller's ratchet model.

The genetic hitchhiking model predicts that there should be selection for null alleles after deleterious mutations have been fixed on the *Y* chromosomes and dosage tolerance (not necessarily dosage compensation) has evolved. One mechanism for inactivating *Y*-linked genes is the permanent insertion of a transposable element. Because the mutation rate via transposable element insertion can be much greater than the normal mutation rate, this process could act to rapidly inactivate accumulated non-null *Y*-linked mutations and result in the rapid accumulation of new fixed mutations on the neo-*Y* chromosome. The hitchhiking model predicts fixation (on the *Y* chromosome) of transposon-inactivated genes, whereas the ratchet model, acting alone, predicts nonfixation.

Testing the hitchhiking and Muller's ratchet models: An indirect test of the models could be based on the fact that the genetic hitchhiking model predicts that breakdown in the activity of a neo-*Y* should not necessarily be coupled with the evolution of dosage compensation. Because the distal 10% of the neo-*Y* in *D. miranda* is known to be non-dosage compensated (STROBEL, PELLING and ARNHEIM 1978), the hitchhiking model predicts that many *Y*-linked loci in the distal 10% of the neo-*Y* should be fixed for null alleles, *i.e.*, sex linkage should be observed for loci in this region. The ratchet model predicts that few if any of these loci will be found to be fixed for null alleles.

A direct means of testing both the hitchhiking and Muller's ratchet models would involve translocations in a model system such as *D. melanogaster*. For example, suppose a neo-*Y*/neo-*X* system analogous to that observed in *D. miranda* were artificially produced in a *D. melanogaster* model system. Different sized translocations could be set up in different treatment populations. Such stocks could be maintained indefinitely and the changes in *X* and *Y* activity could be monitored. This type of experiment would take thousands of *Drosophila* generations (3–4 human generations) to come to fruition, but the simplicity of maintaining the stocks would seem to make the experiment worthwhile.

The idea that dosage tolerance rapidly evolves when males are permanently hemizygous, could also be tested in the laboratory. Translocation of a small segment of an autosome to the *X* chromosome would produce dosage imbalance in males (with the corresponding section of the autosome deleted), since prior experiments demonstrate that such translocations are not dosage compensated by virtue of their linkage to the *X* chromosome. If the ideas presented here are correct, then enhanced output of the neo-*X* genes should rapidly evolve, as well as dosage tolerance.

The relative importance of Muller's ratchet and genetic hitchhiking: The principal factor promoting

the accumulation of deleterious genes on the *Y* chromosome is probably Muller's ratchet. As long as the chromosome (segment)-wide mutation rate is large relative to the average selective disadvantage of heterozygous *Y*-linked mutations, the ratchet process will operate. The hitchhiking process complements Muller's ratchet in three ways. First, it speeds the rate at which the ratchet turns, especially immediately after the *X* and *Y* chromosomes stop recombining. The increased speed of Muller's ratchet is brought about directly, by fixing more heavily mutated *Y* chromosomes, and indirectly by reducing the effective population size of the male population (MAYNARD SMITH and HAIGH 1974). Second, hitchhiking facilitates the fixation (on the *Y* chromosome) of *Y*-linked mutations, and thereby produces selection for dosage tolerance/compensation on a single locus basis. And third, hitchhiking can account for at least a partial breakdown in *Y* chromosomes (segments) that are too small to be broken down by the Muller's ratchet process.

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