Why Sex and Recombination?

N. H. Barton and B. Charlesworth

REVIEW

Most higher organisms reproduce sexually, despite the automatic reproductive advantage experienced by asexual variants. This implies the operation of selective forces that confer an advantage to sexuality and genetic recombination, at either the population or individual level. The effect of sex and recombination in breaking down negative correlations between favorable variants at different genetic loci, which increases the efficiency of natural selection, is likely to be a major factor favoring their evolution and maintenance. Various processes that can cause such an effect have been studied theoretically. It has, however, so far proved hard to discriminate among them empirically.

Sexual reproduction involves the coming together of genetic material from two parents to form progeny that combine genes from both of them (Fig. 1). As defined in this way, sex is an almost universal phenomenon: there are few groups of higher eukaryotes that have persisted by asexual reproduction for a long period of time (*1–3*), and prokaryotic reproduction in nature involves occasional parasexual events that lead to genetic exchange between different individuals (*4*). If asked why sex is such a widespread phenomenon, most biologists would say that it promotes genetic variability, and hence allows evolution to proceed faster than in its absence. This explanation suffers from several difficulties. First, it is not clear a priori that the heritable variance in fitness (the material for adaptation by natural selection) is significantly increased by sex. Second, the most obvious effect of recombination is to break up favorable sets of genes that have accumulated through selection, leading to a recombination load (Fig. 2B) (*5*). Similarly, segregation of genes at a single locus eliminates heterozygotes that may be favored by selection. These forces should cause sex and genetic recombination to be eliminated from a population at equilibrium under selection alone. Third, in organisms with anisogamy (male and female gametes), there is a built-in cost to sex. If there are separate males and females, for example, a mutation that causes females to produce only daughters, but has no other effect, will initially double in frequency in each generation (this is often termed the cost of sex) (Fig. 2A) (*6, 7*).

These difficulties have inspired generations of evolutionary biologists to develop explicit theoretical models of how sexual reproduction, with its consequences for Mendelian segregation and genetic recombination, may confer advantages that outweigh its disadvantages. As a result of work over the last three decades, there is reasonable confidence that the major population genetic processes that potentially yield an advantage to sex are understood (*8–11*). Moreover, models that follow the fate of modifier genes allow movement beyond arguments based on group-level selection, quantification of the intensity of selection for sex and recombination, and identification of the key variables determining such selection. There is little confidence, however, about which of the various possibilities actually plays a role in either the initial evolution of sex or its maintenance in contemporary species. This uncertainty reflects a wider ignorance of the causes of genetic variation in nature and of how genetic variants interact to determine fitness.

Paradoxically, it may be easier to explain the initial origin of sexual reproduction than its maintenance in higher organisms. A relatively slight advantage of sex could cause its evolution in organisms that lack a specialization of germ cells into male and female, whereas anisogamous sexual populations are highly vulnerable to invasion by asexual variants (Fig. 2A) (*6, 8*). Similarly, the maintenance of genetic recombination does not necessarily require a large selective advantage since a modifier that reduces the frequency of recombination does not gain an automatic transmission advantage. In some cases, special mechanisms, such as the requirement for a maternal and a paternal set of homologous genes imposed by genomic imprinting in mammals (*12*), mean that sex is necessarily maintained. But the occurrence of parthenogenetic species among taxa of lower vertebrates, invertebrates, and flowering plants shows that asexuality is mechanistically possible and has evolved independently many times.

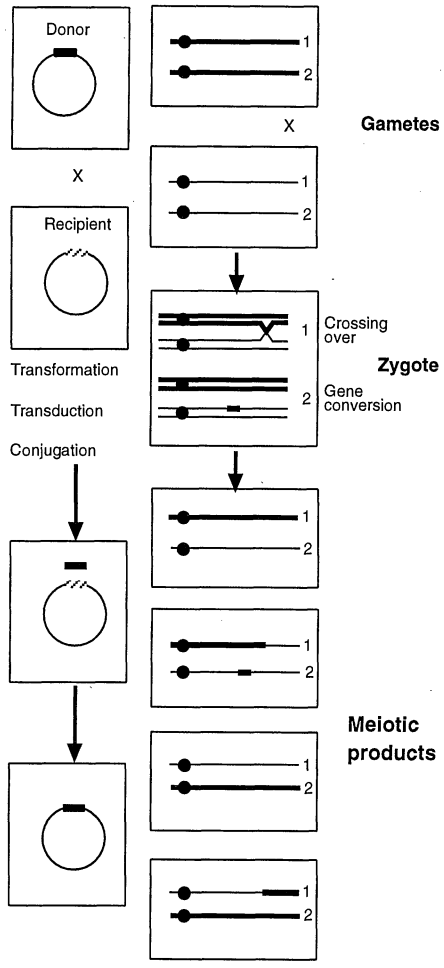

Fig. 1. Parasexual reproduction in a prokaryote (left), and sexual reproduction in a primitive eukaryote (right). In the prokaryote, a segment of DNA from the donor cell (heavy line) is transferred into the recipient cell by transformation, transduction, or conjugation. Recombination with the homologous segment in the recipient (striped line) allows the transferred donor segment to become integrated into the recipient's genome. In the eukaryote, haploid gametes fuse to form a transient diploid zygote, which generates haploid progeny by meiosis. The life cycle is completed by the fusion of gamete cells, which differentiate from mitotically generated descendants of these progeny. There are two chromosomes in the haploid genome, designated by the numbers 1 and 2; their centromeres are indicated by the filled circles. DNA from the two parental gametes is denoted by heavy and thin lines. Recombination of genes from the parents can occur by crossing over, gene conversion, or independent segregation of the centromeres of chromosomes 1 and 2.

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In the vast majority of cases, asexual taxa seem to persist for much shorter periods of evolutionary time than their sexual relatives [chapter 4 in (*8*)]. This is consistent with the view that a successful modification of female germ cell production to allow parthenogenesis is difficult to accomplish and that group-level selective disadvantages to asexual populations may cause their more rapid extinction. The distribution of asexuality among taxa could then reflect a dynamic equilibrium between the extinction and occasional reestablishment of asexual lineages [chapter 4 in (*8*); (*13*)]. But the life cycles of organisms such as *Daphnia* and aphids, with an alternation of asexual and sexual generations, are hard to explain in the absence of within-population advantages to sex [chapter 4 in (*8*); (*14*)].

What advantages might sex confer? It has been suggested that the function of meiotic recombination is to provide a template from which intact genetic information can be recovered (*15*). Similarly, it might be the case that the function of crossovers is primarily to ensure proper disjunction at meiosis, and only incidentally to cause genetic recombination [chapter 5 in (*8*); (*16, 17*)]. While the origin of recombination may have been facilitated by the existence of mechanisms for repair and chromosomal segregation [chapter 1 in (*8*)], and while these processes may now partly constrain recombination (*18, 19*), we do not find such explanations sufficient [see the careful critique in (*17*)]. Recombination between maternal and paternal homologs is not essential for repair of DNA, except for double-strand breaks (*18, 19*); in addition, double-strand breaks are actively induced during meiosis (*18*), which seems odd if meiotic recombination functions to repair them. Localization of crossovers and mechanisms for achiasmate segregation of chromosomes allow recombination to be effectively eliminated without causing nondisjunction (*8, 17*). In addition, these processes cannot readily explain the observed large differences in the frequency of recombination per nucleotide base, even among closely related taxa (*8, 20*). Finally, the evolutionary degeneration of Y chromosomes, which are sheltered from recombination, demonstrates that genetic recombination is necessary to preserve the long-term fitness of a large genome (*21*). Given the existence of abundant genetic variation within species with respect to rates of genetic recombination (*22*), this implies selection against modifiers that prevent recombination.

We therefore concentrate on population genetic explanations that rely on the interaction between selection and variation. If genotypes vary in their use of limiting resources, segregation and recombination can increase the number of surviving offspring by reducing competition among family members or by increasing the family's probability of producing a successful offspring (*8, 14, 23*). However, competition between siblings is confined to certain organisms. In general, any process that only works with certain types of population structure or ways of life cannot explain the ubiquity of sex and recombination (although it might contribute to differences between groups).

If interactions between relatives are excluded, the effect of sex must be mediated by its effect on the distribution of fitnesses in the population as a whole. Crucially, there can only be such an effect if certain gene combinations are present in excess—that is, if there are statistical associations between genetic variants. With random mating, Mendelian segregation eliminates deviations from Hardy-Weinberg genotype proportions that reflect associations between alleles at the same locus, whereas recombination breaks down associations between variants at different loci (linkage disequilibrium). In diploid organisms, the breakdown of nonrandom associations of both kinds may be important in creating an advantage to sexual versus asexual reproduction, but only the between-locus effects are relevant to recombination. [Note that departures from either random mating (*24*) or Mendelian segregation (*25*) can give an advantage to recombination.] Because we need to explain both sex and recombination and because within-locus effects are unimportant for haploid organisms, where sexual reproduction originated, we shall focus on between-locus effects.

The effects of sex and recombination on the distribution of fitnesses among individuals in a population depends on the extent of nonrandom associations among genes and on interactions between the genes that influence fitness. First, suppose that selection acts primarily to alter linkage disequilibrium, by favoring certain gene combinations (epistasis), rather than to change allele frequencies. If such selection is constant over time, recombination merely breaks up favorable combinations and is selected against in randomly mating populations (Fig. 2B). Recombination can be selectively advantageous if different gene combinations are favored in different generations [chapter 6A in (*8*)]; here, recombination is advantageous because it impedes the population's response to fluctuating epistasis. However, such models only work if the relevant parameters are delicately adjusted and if epistasis is strong; they are thus unlikely to be of general importance (*26*). It has been argued that coevolution between species (such as between host and parasite) may produce appropriate fluctuations in epistasis (*27, 28*) by generating endless cycles in genotype frequencies at loci controlling host susceptibility and parasite virulence [an example of Red Queen coevolution (*29*)]. The theoretical basis for this may, however, be questioned. Although selection for sex and recombination can be generated in simulations of host-parasite coevolution, this may reflect the effects of directional selection on allele frequences, which we discuss next.

The increase in mean fitness of a population because of natural selection is proportional to the additive genetic variance in fitness—that is, the component of variance that contributes to the correlation between parents and offspring [chapter 2 in (*30*)]. Hence, if sexual reproduction increases the additive genetic variance in fitness, it will increase the rate of adaptation of the population (*31, 32*). Moreover, modifiers that increase the frequency of sexual reproduction or recombination will tend to become associated with genes that are favored by selection, and so will themselves increase (*33–37*). Thus, the widely held intuition that sex is favored because it facilitates adaptation by natural selection is valid, at both the level of the group and the individual, provided that sex does indeed increase additive fitness variance. Theoretical

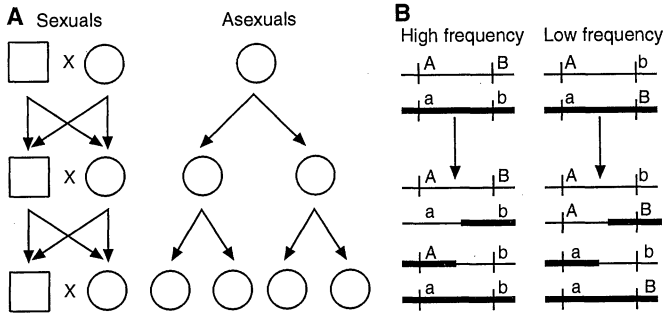

Fig. 2. (**A**) The cost of sex in a species with males (squares) and females (circles). If asexual females have the same family size as sexuals, but produce only daughters, their numbers relative to sexual females will double each generation. (**B**) Recombination load. If the two loci shown interact in their effects on fitness, such that allele A interacts well with B but poorly with b, and vice versa for a, the frequency of the double heterozygote AB/ab (in which recombination reduces the frequency of AB and ab) will be greater than that of Ab/aB (where recombination has the reverse effect) in a randomly mating population. Recombination will thus have the net effect of reducing the frequency of the favored gamete types, AB and ab, and so will reduce the mean fitness of an equilibrium population.

analysis has shown that this requires negative associations among alleles at different loci, such that favorable genes tend to be found in different individuals more often than is expected by chance. Recombination (or segregation) is then advantageous, because it allows favorable alleles to come together within the same individuals (*30*).

Why should there be a seemingly perverse tendency for advantageous genes to be scattered separately through the population? The first possibility is that selection actively favors negative associations among favorable alleles—termed negative or synergistic epistasis. With this form of interaction, the effect on fitness of a deleterious allele increases, the larger the number of deleterious alleles present at other loci; conversely, as more loci acquire favorable alleles, fitness increases by a diminishing factor. With weak selection, the strength of selection for recombination can be simply related to the effect of recombination on the mean and variance of the logarithm of fitness (*36*). The immediate effect of recombination is to reduce mean log fitness, because it breaks up the negative gene combinations favored by epistasis. This is counterbalanced by the increased variance in log fitness which, in the longer term, increases the population mean fitness by speeding up the response to selection (Fig. 3). Synergistic epistasis must not be too strong, because then the immediate recombination load outweighs the indirect advantage of increased fitness variance; the direction of epistasis must also not vary too much across loci (*37*). This theoretical account applies whether selection eliminates deleterious alleles produced by mutation in a constant environment (*34, 37–39*) or tracks changing optima of traits subject to stabilizing selection in a fluctuating environment (*31, 35, 40–42*).

The key problem with accepting this model as a general explanation of sex and recombination is the lack of strong evidence that epistasis is synergistic (*43*). In addition, for sexual reproduction to be maintained against the cost of sex in a diploid organisms with separate sexes, the rate of input of deleterious mutations under the mutational model must be so high that the mean number of new mutant alleles in a new zygote is about one per generation (*39*). The magnitude of this parameter is currently a controversial issue (*44*), but may well be less than this. Similarly, fluctuating environment models demand a high level of selective elimination and large excursions in the optima of the traits subject to stabilizing selection (*35, 40*).

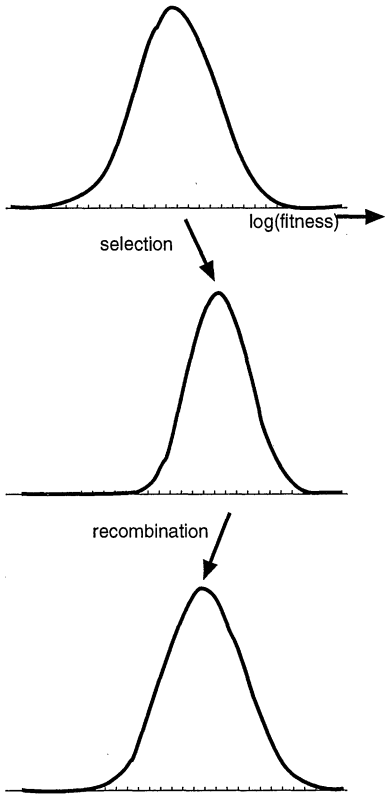

Fig. 3. The distribution of the logarithm of fitness in a population changes as a result of selection and recombination. Selection increases the mean log fitness by an amount equal to the additive genetic variance in fitness [chapter 2 in (*30*)]. If selection favors negative associations, it generates negative linkage disequilibria, which reduce the variance in log fitness, and hence the future response to directional selection. Recombination causes an immediate reduction in mean log fitness by breaking up favored gene combinations, but facilitates future adaptation by increasing the variance in log fitness. It is the balance between these opposing forces that determines whether recombination will be favored (*36*).

Alternatively, negative associations may be generated by the random sampling of genotype frequencies in finite populations. Morgan (*45*), Fisher [chapter 6 in (*30*)], and Muller (*46*) pointed out that favorable mutations that arise in different individuals can only be brought together by recombination. Hence, an asexual population must fix favorable mutations one by one, whereas a sexual population can establish them more rapidly by bringing them together (Fig. 4). The Fisher/Muller effect is a consequence of random sampling of genotypes; even in a very large population, few if any favorable mutations are produced at each locus in each generation, and so new favorable mutations tend to occur in separate individuals.

This effect is not confined to new mutations: in any finite population, random drift leads to negative associations between selectively favorable genes, yielding an advantage to recombination at the level of both population and individual [the Hill-Robertson effect; (*47*)]. However, selection must be strong and widespread for this to be important (*48*). A particularly powerful effect of this kind is generated by the maintenance of deleterious mutations by recurrent mutation. In the absence of recombination, a newly arisen favorable allele can usually become fixed only if it arises in an individual free of deleterious mutations at other loci. If the frequency of such mutant-free individuals is low, the rate of adaptive evolution in a nonrecombining population is greatly reduced (*30*), and such a population may suffer a reduced probability of long-term survival (*49–51*). In contrast, when random drift is associated with the spread of new mutations at more than one locus through a very large sexual population, the effect is only appreciable when favorable alleles at several loci are segregating simultaneously, which requires high rates of gene substitution (*48*). Recombination might gain a greater advantage in a subdivided population because of drift within small local demes, but many species with relatively high rates of recombination lack significant population subdivision [for example, *Drosophila melanogaster*; chapter 5 in (*52*)].

A somewhat different effect of finite population size in combination with deleterious mutations is represented by Muller's ratchet (*53–55*). With recurrent deleterious mutations at many loci, a population can be characterized by the frequencies of genomes containing 0, 1, 2, and so forth, mutations. If the frequency of the mutational class containing the lowest number of mutations is sufficiently small, it will be lost from the population after a finite

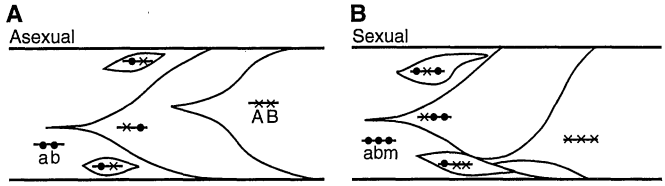

Fig. 4. (**A**) With asexual reproduction, favorable mutations must be established sequentially. For example, if allele A is destined to replace a, then any favorable alleles that occur at other loci (B, for instance) can only be fixed if they occur within a genome carrying A (*30, 46*). (**B**) With sexual reproduction, favorable mutations at different loci can be combined; this leads to an advantage to modifiers that causes sex and recombination. A favorable allele B that occurs with the unfavorable allele a can only be fixed if it can recombine into association with A; if this requires that a modifier allele M be present, then that modifier will also tend to increase by hitchhiking (*48, 72*).

number of generations. If there is no opportunity for genetic recombination, this class cannot be reconstituted and will be replaced by the class with one more mutation. This class is now vulnerable to stochastic loss in the same way. There is thus a repetitive process of loss of successive classes with minimum numbers of mutations. This leads to a decline in the fitness of a nonrecombining or asexual population, which can be substantial even in large populations if the mutation rate per genome is large enough. Because only a low level of recombination is sufficient to halt the ratchet in large populations (*55–57*), it is unlikely to be of significance in relation to the evolution of high levels of recombination. However, it may create a long-term advantage for sex.

The results described above show that there is no shortage of mechanisms by which sexual reproduction and genetic recombination may be favored by natural selection, although some of them seem to be ruled out as general mechanisms. Critical tests to discriminate between the alternative theories have been hard to devise. A popular approach is to compare the ecological correlates of sexual versus asexual species (*58*). This approach has shown that asexual taxa tend to be associated with low density, as at the margins of species ranges, a pattern which has been used to support hypotheses that invoke biotic interactions within or between species (*58*). Unfortunately, the probability that an asexual variant is established in a population is affected by many factors: for example, the need for sexuals to find mates (*59*) or the protection of local adaptations against gene flow (*60, 61*). Comparative patterns of this kind thus do not help to distinguish between alternative advantages to sexual reproduction.

More direct comparative tests of the predictions of specific hypotheses are potentially more fruitful, but considerable care needs to be used in their interpretation. For example, there have been several attempts to test host-pathogen models involving cycling of resistance alleles, by comparing parasite infestations in common and rare asexual clones. The naïve expectation is that the dynamics of infection should cause rare genotypes to be less infected than common ones. This has been found to be true in some cases, but not others (*62*). Theoretical analysis of the time lags between cycles of allele frequencies in host and pathogen shows that a common clone is, in fact, expected to be disproportionately infected only half the time, so that either pattern is consistent with the model (*62*). Unambiguous testing of the models is therefore often difficult to achieve. It also remains to be established whether cases of lower resistance of asexuals reflect genetic effects that are specific to pathogen resistance, and evidence for cycling of alleles is as yet scanty [but see (*63*)]. Much more detailed information on the population biology and genetics of the host-parasite interactions involved in these cases is needed before firm conclusions can be drawn.

Another approach is to compare by experimental manipulation the fitnesses of sexual and asexual, or recombinant and nonrecombinant, progeny. Extensive studies of the first kind have been carried out on grasses by Antonovics and co-workers, exploiting the fact that sexual progeny are produced through seed and asexual progeny from the same parents can be produced vegetatively (*64–66*). These results have successfully demonstrated a substantial advantage to the sexual progeny, though this may in part reflect the fact that plant viruses can be transmitted through vegetative propagules but not through seed (*67*). Studies of evolution in experimental populations of yeast have demonstrated an advantage to sexually reproducing strains over asexual strains under some conditions, but it is hard to identify the causes of this advantage (*68, 69*).

In contrast, experiments in *Drosophila* have consistently demonstrated that nonrecombinant chromosomes confer a lower fitness than recombinant chromosomes (*70*). This is consistent both with the synergistic epistasis models for an advantage to recombination and with the existence of a selection pressure to reduce recombination rates due to an equilibrium between epistatic selection and recombination (Fig. 2B). These two possibilities could be distinguished by measuring the effect of recombination on genetic variance in fitness, because a large effect on variance relative to that on the mean is predicted by the first class of model, and a small effect by the second class (*70*).

Perhaps the most fruitful way forward is to concentrate on determining whether the assumptions of the alternative models are met. It should be possible to ascertain whether genetic polymorphisms for parasite resistance indeed undergo cycling of the periodicities required to generate advantages to sex and recombination, and whether the genetic variance in fitness associated with such polymorphisms is sufficiently high to confer a substantial advantage to sex and recombination. It should also be possible to determine the per genome rate of mutation to deleterious alleles in representative higher organisms, and to determine whether the log fitness of genomes that are accumulating mutations declines faster than linearly, as demanded by the synergistic mutational hypothesis. Determination of the genome-wide rate of selectively favorable gene substitutions would shed light on the role of Hill-Robertson effects in promoting increased recombination. Other aspects of the models are more difficult to test; for example, determining the extent of fluctuations in the optimum values of quantitative traits in natural populations requires many years of patient field work. It should be stressed that the various hypotheses are not mutually exclusive (*71*), so that incremental progress is likely to be made by accumulating evidence for or against specific models, rather than by experiments that discriminate decisively between alternative hypotheses.

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The Evolutionary Dynamics of Sex Determination

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REVIEW

There is substantial cytogenetic data indicating that the process of sex determination can evolve relatively rapidly. However, recent molecular studies on the evolution of the regulatory genes that control sex determination in the insect *Drosophila melanogaster*, the nematode *Caenorhabditis elegans*, and mammals suggest that, although certain sex determination regulatory genes have evolved relatively rapidly, other sex determination regulatory genes are quite conserved. Thus, studies of the evolution of sex determination, a process that appears to have elements that undergo substantial evolutionary change and others that may be conserved, could provide substantial insights into the kinds of forces that both drive and constrain the evolution of developmental hierarchies.

The past few years have witnessed a marked reemergence of interest in the evolution of developmental processes. The emphasis of most current studies is on whether the mechanisms described in model systems are conserved in other species. This approach has demonstrated that a large number of basic cellular processes are shared across vast phylogenetic distances (*1*, *2*). One developmental process that has seemed exceptional in this regard is sex determination, which appears to have substantial evolutionary plasticity. This evolutionary flexibility is surprising, because the regulation of sexual differentiation does not appear to be genetically any simpler than that of other developmental processes. Indeed, changes in sex determination would appear to face an additional evolutionary obstacle: As discussed below, in species with heteromorphic sex chromosomes, modifications in the control of sex determination often have deleterious side effects. By comparing how a range of animal species confront these problems, insight is being gained into the constraints on how sex determination mechanisms evolve.

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Classical View: Sex Determination Evolves Rapidly

Cytogenetic studies during the first half of this century showed that there are variations in sex chromosome systems among animal species, even those that are closely related, suggesting that sex chromosomes may evolve rapidly (*3*, *4*). Moreover, subsequent genetic studies showed that sex determination can be radically different in species whose chromosomal complements are apparently identical, thus further widening the possible variations in sex determination mechanisms (Table 1).

Such cytogenetic studies even identified species in which there are intraspecific variations in the mechanism of sex determination. For example, in the "standard" strains of *Musca domestica*, the housefly, sex determination is controlled by a masculinizing Y-linked gene (*M*). These strains are thus XY:XX. However, in other natural populations of this species, the chromosomes of males and females are indistinguishable. It has been genetically demonstrated that in males of those strains, *M* is autosomal (*5*). Finally, in still other populations, the autosomal *M* factor is homozygous in both males and females. Unisexuality is avoided because females carry a dominant female-determining gene (F^D), which is able to override the presence of *M* [reviewed in (*6*)]. Similarly, in natural populations of the wood lemming *Myopus schisticolor*, there are both normal males (XY) and females (XX) as well as females with a Y chromosome (X*Y females). Generally, in mammals, maleness is determined by the presence of the Y-linked gene *Sex-determining region Y* (*Sry*) (see below). In *Myopus*, however, although the Y chromosome carried by these X*Y females contains a normal *Sry* gene, they develop as females because the X* chromosome is able to overcome the masculinizing effect of the Y (*7*). Because close relatives of these exceptional species do not have similar polymorphisms, these observations provide additional evidence that sex determination can sometimes change rapidly.

These kinds of observations led to the view that the genetic systems that control sex determination, taken as a whole, may lack the "respectable antiquity" of the genetic machinery involved in other basic developmental processes (including specification of