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ACCUMULATION OF NONFUNCTIONAL GENES ON SHELTERED CHROMOSOMES

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INTRODUCTION

It is well known that the X- (or Z-) chromosomes of higher organisms have many gene loci at which visible mutations may occur, while the Y- (or W-) chromosomes have few, if any, such loci, except in those organisms in which the sex chromosomes are not well differentiated (see Dronamraju 1965; Mittwoch 1967, for recent reviews). It is also known that in a species with the XY sex determination, the XO individuals can generally survive, while the YO individuals cannot. These facts suggest that X-chromosomes are essential to the development of organisms, while Y-chromosomes may be dispensable. Of course, this does not mean that there are no functional genes on Y-chromosomes. On the contrary, recent studies indicate that the Y-chromosomes of many organisms have strong sex-determining genes; the *Drosophila* Y-chromosome, which lacks such genes, may be exceptional in this respect. Also, Y-chromosomes are known to have important genes, such as those controlling fertility (Stern 1929; Hess and Meyer 1968), ribosomal RNA synthesis (Ritossa and Spiegelman 1965), etc. The RNA-DNA hybridization experiments have shown that a large number of cistronic loci in the Y-chromosome are concerned with both fertility control and ribosomal RNA synthesis in *Drosophila* (Hennig 1968; Ritossa and Spiegelman 1965).

Nevertheless, it is almost certain that Y-chromosomes are lacking in many genes essential for life which are present on X-chromosomes. As an extreme example, XO females in mice are not only viable but also fertile (Cattanach 1962). Since the X- and Y-chromosomes are believed to have evolved from a homologous pair of autosomal chromosomes in their ancestral organism (Darlington 1937; Ohno 1967), there must have been a preferential inactivation of the genes on the Y-chromosome during the evolutionary process. As will be discussed later, this inactivation of genes would not occur at certain kinds of gene loci.

Muller (1914) was probably the first to put forward a mechanism to

explain the preferential inactivation of the Y-chromosome. He argued that the gene loci on the Y-chromosome are always kept heterozygous, so that any lethal mutations occurring at these loci are sheltered by the wild type allele at the homologous loci on the X-chromosome, while the lethal mutations occurring on the X-chromosome are eliminated in the homogametic sex, where the lethal mutations may become homozygous. Therefore, he thought, the accumulation of lethal genes would occur on the Y-chromosome. His argument was, however, intuitive and not based on any quantitative study of the frequency changes of lethal genes on the Y-chromosome. Later Fisher (1935) examined the probability of accumulation of lethal genes on the Y-chromosome in large populations and showed that this probability is extremely small. On this ground he rejected Muller's hypothesis. Recently, Frota-Pessoa and Aratangy (1968) studied the equilibrium frequency of lethal genes on the Y-chromosome and indicated that it is greatly increased when there is inbreeding due to consanguineous matings. Nevertheless, he did not show that fixation of lethal genes on the Y-chromosome could really occur.

Fisher's and Frota-Pessoa's mathematical treatment is based on the model of infinite population size. Natural populations are, however, always finite. Thus, it is necessary to examine the probability of accumulation of lethal or nonfunctional genes in finite populations. In the following I shall show that this probability is quite high in small populations, provided that there is little recombination between the sheltered (Y) and sheltering (X) chromosomes. In this connection, it may be noted that there are several types of sheltered chromosomes other than Y-chromosomes, such as the so-called B-chromosome, the chromosome responsible for the short style in heterostyled plants, and inversion chromosomes artificially maintained heterozygous.

INHIBITED RECOMBINATION BETWEEN THE SHELTERED AND SHELTERING CHROMOSOMES

Let us first consider the case of inhibited recombination between the sheltered and sheltering chromosomes. In most organisms with well-differentiated sex chromosomes, there appears to be virtually no recombination between the X- and Y-chromosomes or the differentiated segments of these chromosomes. We will consider a particular stage of evolution of the sex chromosomes, in which the X- and Y-chromosomes are well differentiated with respect to sex-determining genes but are still homologous and carry the same loci with respect to other genetic functions. The evolutionary interdependence of sex determination and inhibition of recombination between the X- and Y-chromosomes has been studied by Nei (1968*a*, 1968*b*; 1969*b*).

Consider a lethal gene a and its allelic normal gene A at a homologous locus of the X- and Y-chromosomes. Let x_f and x_m be the frequency of a on the X-chromosome in the female and male gametes, respectively, and y be

TABLE 1
FREQUENCIES AND FITNESSES OF GENOTYPES IN MALES AND FEMALES

	Males			
Genotype	X^AY^A	X^AY^a	X^aY^A	X^aY^a
Frequency	$(1-x_{f2})(1-y)$	$(1-x_{f2})y$	$x_{f2}(1-y)$	$x_{f2}y$
Fitness	1	$1-h$	$1-h$	~~X^AX^A~~

	Females		
Genotype	X^AX^A	X^AX^a	X^aX^a
Frequency	$(1-x_{f1})(1-x_m)$	$(1-x_{f1})x_m+x_{f1}(1-x_m)$	$x_{f1}x_m$
Fitness	1	$1-h$	$1-s$

the frequency of a on the Y-chromosome. In a randomly mating population the genotype frequencies in females and males are expected to be as given in table 1. The difference between x_{f1} and x_{f2} are caused by the sampling process, and the expected values of x_{f1} and x_{f2} are the same and equal to x_f. We designate the relative fitnesses of genotypes AA, Aa, and aa by 1, $1-h$, and $1-s$, respectively. For a completely lethal gene, $s=1$, and for a semilethal gene, $1>s>0.5$. We designate the population size by N, and assume that the sex ratio is 0.5. We further assume that the mutation rate from A to a, u, is the same for both the X- and Y-chromosomes, and the reverse mutation is negligible. For obtaining the probability of fixation of a lethal mutation on the Y-chromosome, we need first to know the mean ($M_{\delta y}$) and variance ($V_{\delta y}$) of the change of y per generation (see Kimura 1962).

$M_{\delta y}$ can easily be obtained from table 1, and becomes

$$M_{\delta y}=-[h+x_{f2}(s-2h)]y(1-y)/\overline{W}_m, \tag{1}$$

where $\overline{W}_m=1-hx_{f2}-[h+x_{f2}(s-2h)]y$. The variance of the change in y is given by

$$V_{\delta y}=2y(1-y)/N, \tag{2}$$

since there are only $N/2$ Y-chromosomes in a population of size N. For a lethal gene, x_{f2} is expected to be generally very small if u is of the order of 10^{-5}. Thus, if h is small, as is usually the case, $\overline{W}_m$ is almost unity and $M_{\delta y}$ is approximated by $-[h+x_{f2}(s-2h)]y(1-y)$.

In equilibrium populations, the expected values of x_{f1}, x_{f2}, and x_m are close to each other, though x_m could be slightly smaller than x_{f1} and x_{f2} when y is large. The probability distribution of the mean (x) of x_{f1}, x_{f2}, and x_m is approximately given by

$$\phi(x)=C\,e^{-4N_ehx-2N_e(s-2h)x^2}x^{4N_eu-1}, \tag{3}$$

where C is a constant such that $\int_0^1\phi(x)dx=1$, and N_e is the effective population size for sex-linked genes and equal to $3N/4$ (see Wright 1937; Nei 1968c). The above formula indicates that in small populations x is 0 most of the time and is only occasionally significantly larger than 0, if the mutation rate from A to a is of the order of 10^{-5}. For example, if $h=0$, $s=1$, and $u=10^{-5}$, the probability that none of the X-chromosomes in

the population has lethal gene a is .99 when $N = 10$ and .98 when $N = 100$. Therefore, in small populations the lethal mutations with $h = 0$ would behave just like a neutral gene and be fixed in the population with a probability close to $2/N$.

In larger populations, or when Nu is larger than those in the above examples, the effect of lethal genes on the X-chromosome on the probability of fixation of a lethal gene on the Y-chromosome becomes important. It is not easy to determine the exact probability, but the approximate probability can be obtained by assuming that x_{f2} is constant and equal to the mean of x in (3), that is, $\bar{x} = \int_0^1 x\phi(x)\,dx$. If $h = 0$, $\bar{x}$ is

$$\bar{x} = \frac{\Gamma(1.5Nu + 0.5)}{\sqrt{1.5Ns}\,\Gamma(1.5Nu)}, \tag{4}$$

approximately (see Wright 1937; Nei 1968*c*). On the other hand, if $h >> \sqrt{us}$ and $4N_e h >> 1$, $\bar{x}$ is u/h, approximately (Nei 1968*c*, 1969*c*).

Replacing x_{f2} by $\bar{x}$ in $M_{\delta x}$ and inserting $M_{\delta x}$ and $V_{\delta x}$ into Kimura's (1962) general formula for the probability of fixation of mutant genes, we have

$$u(y_0) = (e^{NSy_0} - 1)/(e^{NS} - 1), \tag{5}$$

where $u(y_0)$ is the probability of fixation of lethal gene a on the Y-chromosome, given that the initial gene frequency is y_0, and $S = h + \bar{x}(s - 2h)$.

Strictly speaking, the above formula is expected to give a slight underestimate of the probability of fixation, since the real mean of x_{f2} could be slightly smaller than $\bar{x}$ when y is large. This is because more lethal genes on the X-chromosome would be eliminated in males when y is large. Thus, a Monte Carlo simulation was conducted in order to examine the degree of approximation of the above formula. Parameters of $N = 100$, $s = 1$, $h = 0$, $u = 0.0001$ were employed. Selection and mutation were assumed to occur deterministically. The scheme of selection was the same as that given in table 1. In each generation, after selection and mutation had occurred, pseudo-random numbers were generated and used to determine the values of x_{f1}, x_{f2}, x_m, and y in the next generation. Four hundred replicate runs were performed for each initial value of y. The initial values of x_{f1}, x_{f2}, and x_m were given according to formula (3). That is, the expected frequencies of gene frequency classes 0, 1/150, 2/150, etc., were computed by formula (3), and varying initial values of x_{f1}, x_{f2}, and x_m (0, 1/150, 2/150, . . .) were used according to the expected frequencies. The probabilities of fixation for various values of y_0 are given in table 2, together with the theoretical values obtained by formula (5). It is seen that the values obtained from the simulation are very close to the theoretical values.

If y_0 is $2/N$, $u(y_0)$ is approximately $2S/(e^{NS} - 1)$. In a population of size N, the expected number of mutations per generation is $Nu/2$. Therefore, the rate of fixation of deleterious genes per locus per generation is given by

TABLE 2
PROBABILITIES OF FIXATION OF LETHAL GENES ON THE Y-CHROMOSOME AS OBTAINED BY A MONTE CARLO SIMULATION

y_0	Theoretical	Observed
.05	.045	.043 ± .010
.1	.091	.099 ± .015
.2	.183	.176 ± .019
.5	.474	.461 ± .025

NOTE.—$N = 100$; $s = 1$; $h = 0$; $u = 0.0001$. For each initial value (y_0) of y, 400 replicate runs were performed. The theoretical values were obtained by formula (5).

$$P = NuS/(e^{NS} - 1); \qquad (6)$$

P approaches u when $S \to 0$, agreeing with Kimura's (1968) result that the rate of fixation of neutral mutations is equal to the mutation rate per gamete. In the present case, of course, $S = 0$ does not mean neutral mutations, although they behave effectively as neutral in populations. In table 3 the values of P/u for various values of h, s, and N are given, the mutation rate being assumed to be 10^{-5} in all cases. The value of $\bar{x}$ in S was obtained by formula (4) when $h = 0$, but in the case of $h \neq 0$, it was determined by numerical integration. It is seen that the rate of fixation for $s = 1$ and $h = 0$ is quite high if N is smaller than 4,000, while for $N > 6{,}000$ it is small. In a population larger than 10,000 it is almost impossible for a lethal gene to be fixed on the Y-chromosome, agreeing with the result obtained by Fisher (1935). If $s = 0.5$, the rate of fixation is increased for all values of N, and even with $N = 6{,}000$ this rate becomes appreciable in view of evolutionary time. On the other hand, slight selection against the lethal heterozygotes greatly reduces this rate.

In the above formulation we completely neglected the backward mutation from a to A. Most lethal mutations are presumably frame-shift or nonsense mutations, though missense mutations may also have lethal effects when they occur at those DNA bases which code for the amino acids at active sites of a protein. It has been shown in microorganisms that both frame-shift and nonsense mutations may change so as to restore the original function of the gene with a measurable frequency. Atwood, Schneider, and Ryan (1951) studied the forward and backward mutations of the histidine

TABLE 3
RATES OF FIXATION OF LETHAL GENES ON THE Y-CHROMOSOME (P/u)

N	$s = 1$, $h = 0$	$s = 0.5$, $h = 0$	$s = 1$, $h = 0.02$
10	0.9997	0.9999	0.9030
100	0.9892	0.9923	0.3095
1,000	0.7037	0.7962	3.0×10^{-8}
2,000	0.3416	0.4645	8.3×10^{-17}
4,000	0.0318	0.1017	...
6,000	0.0011	0.0110	...
10,000	3.3×10^{-5}	2.7×10^{-7}	...

NOTE.—All values should be multiplied by the mutation rate, u, which is assumed to be 10^{-5}.

(h) locus of *Escherichia coli* and showed that the backward mutation rate is about 100 times lower than the forward mutation rate ($h^+ \rightarrow h^-$, 2×10^{-6} vs. $h^- \rightarrow h^+$, 3×10^{-8} per cell division). This estimate of backward mutation rate is indeed small compared with the forward mutation rate, but it has a profound effect on the population dynamics of lethal genes on the Y-chromosome. Namely, complete fixation of lethal genes no longer occurs on the Y-chromosome, although the gene frequency for the X-chromosome is hardly affected by the backward mutations. Thus, the gene frequency for the Y-chromosome is expected to attain some stationary distribution at equilibrium in finite populations. This distribution [$\phi(y)$] is again obtained from (1) and (2) by using Wright's (1945) general formula. (The forward and backward mutations are now included in [1].) It is approximately given by

$$\phi(y) = C\, e^{-NS}\, y^{Nu-1}\, (1-y)^{Nv-1}, \qquad (7)$$

where v is the mutation rate from a to A, and $C^{-1} = B(Nu, Nv)\,{}_1F_1(Nu, Nu+Nv, -NS)$, in which $B(\cdot,\cdot)$ and ${}_1F_1(\cdot,\cdot,\cdot)$ stand for the beta and confluent hypergeometric functions, respectively.

Now our problem is: How often is a population fixed with lethal genes at equilibrium? If the probability of a population being fixed with lethal genes is high, the gene could become genetically inert in course of time due to the action of modifier genes or mutations of genes which control the transcription or translation of the locus fixed for the lethal allele. The probabilities of a population being fixed with a and A (f_1 and f_0) are obtained by $2\phi(1-2/N)/(N \cdot Nv)$ and $2\phi(2/N)/(N \cdot Nu)$, respectively (see Wright 1931). Thus, we have

$$f_1 = C\, e^{-NS}/[Nv(N/2)^{Nv}] \qquad f_0 = C/[Nu(N/2)^{Nu}], \qquad (8)$$

approximately. It can be shown that f_1 and f_0 become 1 and 0, respectively, as $Nv \rightarrow 0$, while they both approach 0 when Nu and Nv become infinitely large, as expected.

The values of f_1 and f_0 for various values of h and N are given in table 4, where $u = 10^{-5}$ and $v = 10^{-7}$ are assumed. It is clear that, if $h = 0$ and $N \leqslant 4{,}000$, the probability of a population being fixed with lethal genes is quite high, roughly agreeing with the conclusion obtained from the study of the probability of fixation of a single lethal mutation.

EFFECT OF RECOMBINATION

As discussed elsewhere (Nei 1969*b*), there is no need for preventing the recombination between the X- and Y-chromosomes as long as sex is determined by a single locus or a few closely linked loci. Thus, in yeast where a single locus (a,α) is responsible for sex (mating type) determination, the chromosome carrying the sex-determining gene shows quite frequent intrachromosomal recombinations (see, for example, Mortimer and Hawthorne 1966). Recombination is also known to occur between a pair of the sex-

TABLE 4
PROBABILITIES OF POPULATIONS BEING FIXED WITH LETHAL GENES (f_1) AND THE WILD-TYPE GENES (f_0) AT EQUILIBRIUM

N	s	h	r	f_1	f_0
10	1	0	0	.9902	.0099
100	1	0	0	.9905	.0101
1,000	1	0	0	.9870	.0178
2,000	1	0	0	.9519	.0522
4,000	1	0	0	.4117	.4637
6,000	1	0	0	.0147	.6839
10,000	1	0	0	.0000	.5564
10	1	.02	0	.9886	.0121
100	1	.02	0	.9308	.0695
1,000	1	.02	0	.0000	.9668
10	1	0	.001	.0097	.9898
100	1	0	.001	.0062	.9856
1,000	1	0	.001	.0000	.9346

NOTE.—r denotes the recombination value between the sex-determining and the lethal loci.

factor-carrying chromosomes of the brine shrimp (*Artemia salina,* Bowen 1965) and some teleost fish (*Oryzias latipes,* Aida 1921; *Lebistes reticulatus,* Winge and Ditlevsen 1947) though the recombination frequency is generally low. When there is recombination between the X- and Y-chromosomes, the lethal genes accumulated on the Y-chromosome may be exchanged with the normal genes on the X-chromosome. This will prevent complete fixation of lethal genes on the Y-chromosome, even if there is no backward mutation. Let us now examine the probabilities of a population being fixed with gene a and A at equilibrium with recombination occurring, that is, f_1 and f_0.

Let M and F be the male- and female-determining genes or gene complexes on the Y- and X-chromosomes, respectively, and r be the recombination value between the loci M-F and A-a. The genotypes X^AX^A, X^AX^a, etc. in table 1 are now replaced by FA/FA, FA/Fa, etc. Only the frequencies of gametes produced by the double heterozygotes FA/Ma and Fa/MA are affected by recombination. They become

	Gamete produced			
Genotype	FA	Fa	MA	Ma
FA/Ma	$(1-r)/2$	$r/2$	$r/2$	$(1-r)/2$
Fa/MA	$r/2$	$(1-r)/2$	$(1-r)/2$	$r/2$

Therefore, the frequency of a on the Y-chromosome in the next generation is given by

$$y' = \{[(1-r)(1-x_{f2})y + rx_{f2}(1-y)](1-h) + x_{f2}y(1-s)\}/\overline{W}_m,$$

where $\overline{W}_m = 1 - (x_{f2} + y - 2x_{f2}y)h - x_{f2}ys$. Hence, noting $\overline{W}_m \approx 1$, we have

$$M_{\delta y} = -r(1-h)(y - x_{f2}) - [h + x_{f2}(s-2h)]y(1-y), \qquad (9)$$

approximately. Again, $V_{\delta y}$ is given by $2y(1-y)/N$. Assuming that x_{f2} is

constant and equal to its mean, $\bar{x}$, as before, and inserting $M_{\delta y}$ and $V_{\delta y}$ into Wright's general formula, the frequency distribution of y is given by

$$\phi(y) = C\, e^{-NSy}\, y^{A-1}\,(1-y)^{B-1}, \tag{10}$$

where $A = Nr\bar{x}(1-h)$, $B = Nr(1-\bar{x})(1-h)$, and $C^{-1} = B(A,B)_1 F_1(A, A+B, -NS)$. Therefore, we have

$$f_1 = C\, e^{-NS}/[B(N/2)^B] \qquad f_0 = C/[A(N/2)^A], \tag{11}$$

approximately.

Some values of f_1 and f_0 are given in table 4. It is seen that only a small amount of recombination (0.1%) drastically changes the value of f_1 and f_0 in small populations and the populations are fixed mostly with normal rather than with lethal alleles. This suggests that any sheltered chromosome that crosses over with its sheltering chromosome has a low probability of accumulation of lethal genes, except at those loci which are closely linked to the sex-determining gene.

DISCUSSION

From the studies mentioned above, it is clear that the accumulation of lethal genes or nonfunctional genes is highly dependent on the effective population size, heterozygous effect of the genes, and recombination values between the sex-determining and the lethal gene loci. Many of the recent studies (e.g., Kerster 1964; Tinkle 1965; Merrell 1968) have indicated that the effective size of natural populations may be quite small, although there is generally some migration among populations. In *Drosophila melanogaster,* Wallace (1966) showed that the allelic frequency of lethal genes on the second and third chromosomes is 0.046 in flies collected from small areas. This strongly suggests that the effective size is quite small, probably less than 2,000 (see Nei 1968*c*). Note that the effective size estimated from the allelic frequency of lethal genes includes the effect of migration between populations. Further, it is possible that the effective size of a population in a rapid process of evolution or speciation is much smaller than that of a stable and nonevolving population, since a new species would often develop from a local or marginal population of its ancestral species.

There is still controversy about the heterozygous effect of lethal genes in *Drosophila.* Crow and Temin (1964), Nei (1968*c,* 1969*c*) and others claim that they are on the average slightly deleterious in heterozygous condition, while Wallace (1966), Dobzhansky and Spassky (1968), and others report that they are slightly beneficial to the heterozygotes. The rate of mutations to lethal alleles per X-chromosome per generation has been estimated to be 0.0026 in *Drosophila melanogaster* (see Crow and Temin 1964). If the lethal genes are all completely recessive and the effective population size is about 2,000, then the expected number of lethal genes fixed per generation on a Y-chromosome of length equal to the X-chromosome (perhaps this was the case before the differentiation of the X- and Y-chromosomes)

is approximately 0.00079 ($= 0.0026 \times 0.3416$). Thus, in a period of one million generations, about 800 loci can become genetically inert. This is a quite rapid process in terms of evolutionary time. If lethal genes are slightly beneficial in the heterozygous state as reported by Wallace (1966) and Dobzhansky and Spassky (1968), the accumulation of lethal genes on the Y-chromosome would be even faster.

On the other hand, if lethal genes reduce the heterozygote fitness even slightly, the probability of accumulation of lethal genes drastically decreases except in extremely small populations. Crow and Temin (1964) and Nei (1968*c*) have analyzed data on lethal chromosome frequencies in natural populations of *Drosophila* and concluded that lethal genes reduce the heterozygote fitness by 1%–1.8% on the average. This, of course, does not mean that there are no completely recessive or overdominant lethals. On the contrary, it seems that there are lethals with varying degrees of dominance from slightly overdominance to rather high degree of partial dominance. If this is the case, those genes which are overdominant or completely recessive would be fixed in the population rather quickly but the others would be fixed only slowly, depending on the degree of dominance and population size. If the effective population size is larger than 1,000, it would be almost impossible for lethal genes with h larger than 0.02 to be fixed in the population.

This would mean that, if the degree of dominance (h) of lethal genes is locus-specific, lethal genes are fixed at certain loci but not at others. On the other hand, if h is the property of a type of mutation, such as nonsense, missense, and frame-shift mutation, rather than the property of genetic loci, then it is possible that lethal genes are accumulated at almost all loci. In this case, of course, the probability of accumulation is slightly reduced, because only those mutations that are almost completely recessive are relevant. At present, we do not know which of the two alternatives is more important. There is some evidence that the degree of dominance depends on the type of mutation. Bernstein and Fisher's (1968) experiment on joint infection of wild type and mutant T4 phages on *E. coli* indicates that nonsense (amber) mutations show a higher degree of dominance (h) than missense (temperature-sensitive) mutations. At any rate, the above argument suggests that lethal or nonfunctional genes can be accumulated at least at certain loci on sheltered chromosomes, even if the heterozygote fitness is reduced by 1%–2% on the average.

So far we have been concerned with lethal mutations. Some mutations, however, do not appear to have lethal effect, even if they do not code for any functional enzymes. This is possible if there are many duplicate genes in the genome (see Nei 1969*a*) or if the enzymes or proteins coded for are not essential to the organism. These nonfunctional mutations are expected to accumulate on a sheltered chromosome more rapidly than lethal mutations, if the heterozygous effect is the same. Functional mutations, whether beneficial or deleterious, would also be fixed on a sheltered chromosome in the same way, if their effect on the heterozygote fitness is small. This sort

of mutations would contribute to the genetic differentiation of the X- and Y-chromosomes.

In organisms with well-differentiated sex chromosomes there is virtually no recombination between the X- and Y- (or Z- and W-) chromosomes. It seems that the inhibited recombination between the X- and Y-chromosomes is a simple evolutionary consequence of tightening the linkage of sex-determining genes, as shown by Nei (1969*b*). If sex is determined by a number of male- and female-determining genes on the Y- and X-chromosomes, respectively, it is essential to prevent the recombination between those sex-determining genes to avoid intersexes. Nei (1969*b*) demonstrated mathematically that a mechanism for preventing the recombination could evolve rather quickly under certain conditions. The present study indicates that the inertness of the Y-chromosome could occur only after the elimination of recombination between the X- and Y-chromosomes.

In some species the Y-chromosome is missing, so that the male and female are XO and XX, respectively. This does not, however, mean that all the genes located on the original Y-chromosome had become nonfunctional before the loss of the Y-chromosome. Under the present model, the sex-determining genes never become nonfunctional. It is likely that in these species the sex-determining genes were transferred to one or more of the autosomal chromosomes by translocation before the rest of the Y-chromosome was lost. In this connection it is of interest to note that the male-determining genes in *D. melanogaster* are located on the autosomal chromosomes (Bridges 1925).

Fisher (1935) considered the nonlethality of homozygotes for the short-style gene in heterostyled plants such as *Primula sinensis* as evidence against the accumulation of lethal genes on sheltered chromosomes. If, however, there occurs recombination between the chromosomes carrying the short-style and long-style genes, lethal genes would not necessarily be accumulated on the sheltered short-style chromosome. Furthermore, if there is any possibility that the short-style plants self-fertilize in nature, the probability of accumulation of lethal genes would be greatly reduced. It is worthwhile to note that a genetically inert region closely linked with the male-determining gene has been discovered in *Lebistes reticulatus* and *Oryzias latipes* by using the technique of sex reversal (Winge and Ditlevsen 1947; Yamamoto 1964).

As mentioned earlier, there are several types of sheltered chromosomes other than Y-chromosomes. Among others, B-chromosomes have been found in a wide range of species of plants and animals. As is well known, B-chromosomes are also genetically inert except for a few genes (see Lewis and John 1963). It seems that the genetic inertness of B-chromosomes may have occurred in a manner similar to that of Y-chromosomes, though a more detailed study is necessary for these chromosomes. Accumulation of nonfunctional genes is also possible at duplicated gene loci on autosomal chromosomes, as briefly discussed by Nei (1969*a*).

SUMMARY

The probability of accumulation of nonfunctional mutations on sheltered chromosomes such as the Y-chromosome in higher organisms is studied by using diffusion approximations in probability theory. It has been shown that this probability is highly dependent upon the effective population size, the heterozygous effect of nonfunctional mutations, and the recombination value between the sex-determining and nonfunctional gene loci. The present knowledge of these three factors, which has been obtained mostly from *Drosophila* studies, suggests that the nonfunctional genes could be accumulated on sheltered chromosomes within a reasonable period of evolutionary time.

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