CONCERNING EQUILIBRIA OF HETEROTIC LETHALS
IN RANDOM MATING POPULATIONS WITH
PARTICULAR REFERENCE TO 1(2)55i
IN *DROSOPHILA MELANOGASTER*¹

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THE introduction of lethal genes into a random mating population has, on the whole, a deleterious effect (that is, an adverse effect on the mean adaptive value of the population). However, if the lethal genes show heterotic effect, they are maintained, and if the zygotic viabilities and/or female fecundities of the lethal heterozygotes are large, the genes tend to increase population productivity within a certain area of gene frequencies and, therefore, have a role in the evolution of the population.

IVES (1945), WALLACE (1950) and PROUT (1954) have reported the spontaneous lethal mutation rate in the second chromosome of *Drosophila melanogaster*. Their estimates are 2.6×10^{-5} , 1.0×10^{-5} , and 1.13×10^{-5} lethal mutations per locus per generation, respectively. IVES (1945) and WALLACE (1950) also estimated the number of second chromosome loci which can mutate to lethals. The estimated numbers were 495 (IVES) and 400 (WALLACE).

STERN and his collaborators (1952) estimated the viability effect of sex-linked recessive lethals in heterozygous condition. Their results show that 27 out of 75 sex chromosome recessive lethals had some heterotic effect on zygotic viability.

It may be assumed that the lethal mutation rate is 1.13×10^{-5} per locus per generation, which is PROUT's (1954) estimate (used because it is intermediate among the three estimates) and that the number of loci which can mutate to lethal is 1000 in *Drosophila melanogaster*.

If one third of the lethals show heterosis (STERN, CARSON, KINST, NOVITSKI, and UPHOFF 1952), each fly in each generation has a probability of 0.0038 ($= 1.13 \times 10^{-5} \times 10^3 \times \frac{1}{3}$) of having a new heterotic lethal mutation. Disregarding genetic drift, which might reduce the above probability estimate by one half, we find that heterotic lethals should accumulate in a population, but the evidence indicates that they do not. Rarely is a single lethal present in more than a trace frequency in a population.

In an attempt to explain this contradiction by ascribing the results to the effect of modifying mutations in the genetic background, we will extend the development of mathematical models, previously used by MUKAI and BURDICK (1959),

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in this report. In addition, population productivity will be defined as a general concept and discussed with respect to lethal heterozygous populations.

MATHEMATICAL MODELS AND RESULTS

Definition of parameters

MUKAI and BURDICK (1959) separated relative viability of lethal heterozygotes into female fecundity (f), male mating ability (m), sperm competitive ability (s), and zygotic viability (v) and defined the following parameters:

Q_n = frequency of lethal heterozygotes (noted as Aa) in the n th generation, aa being lethal.

$1 - Q_n$ = frequency of AA individuals in the n th generation.

Q = frequency of lethal heterozygotes in the equilibrium population.

m = relative mating ability of Aa males, that of AA males being 1.

f = relative fecundity of Aa females, that of AA being 1.

v = relative zygotic viability (hatchability + larval competitive ability + length of larval period) of Aa individuals, that of AA being 1.

s = relative competitive ability of " a " sperms, that of " A " sperms being 1.

n = the number of generations.

In addition to the above notations, the following are added for the purpose of calculation.

P = relative population productivity.

$\Delta m, (\Delta f; \Delta v; \Delta s)$ = increment of change per generation of mating ability (female fecundity, zygotic viability, sperm competitive ability) of lethal heterozygous individuals caused by the epistatic effect of modifying mutations in the genetic background.

c = relative frequency of individuals in which mutations changing the viability of lethal heterozygotes take place at a given locus in one generation.

Models

Lethal genes are of three types with respect to their macrogenetic behavior, that is, autosomal (A), *Drosophila* type sex chromosomal (XY-type) (B), or *Bombyx* and chicken type sex chromosomal (ZW-type) (C).

A. Autosomal lethals:

(1.) *Zygotic viability* (v):—The necessary and sufficient conditions for maintenance of a lethal gene were presented by MUKAI and BURDICK (1959). They showed that when a lethal gene has a heterotic effect expressed in zygotic viability, namely, $v > 1$, this lethal is maintained in the population. The zygotic array in the equilibrium population is as follows: $1/(2v - 1)$ of AA , $(2v - 2)/(2v - 1)$ of Aa , and none of aa .

If a mutation takes place in the genetic background modifying the viability of

the lethal heterozygote (Aa), the following array will be produced:

Genotype:	αAA	βAA	αAa	βAa	aa
Viability:	1	1	v	$v + \Delta v$	0
Frequency:	$\frac{(1-c)}{(2v-1)}$	$\frac{c}{(2v-1)}$	$\frac{(2v-2)(1-c)}{(2v-1)}$	$\frac{(2v-2)c}{(2v-1)}$	0

where α and β (used here and subsequently) denote the original and the mutational genetic background, respectively. If complete dominance of the new mutation is assumed, the zygotic array in the next generation will be as follows:

$$(AA) = 1 - Q_1 = \frac{v}{v + 2(v-1) [v(1-c)^2 + c(2-c)(v+\Delta v)]}$$

$$(Aa) = Q_1 = \frac{2(v-1) [v(1-c)^2 + c(2-c)(v+\Delta v)]}{v + 2(v-1) [v(1-c)^2 + c(2-c)(v+\Delta v)]}$$

The one generation change in frequency of lethal heterozygotes (ΔQ) is as follows:

$$\Delta Q = \frac{2(v-1) [v(1-c)^2 + c(2-c)(v+\Delta v)]}{v + 2(v-1) [v(1-c)^2 + c(2-c)(v+\Delta v)]} - \frac{2v-2}{2v-1}$$

$$= \frac{2(v-1)(2-c)\Delta v}{(2v-1) \{v + 2(v-1) [v(1-c)^2 + c(2-c)(v+\Delta v)]\}} \dots \dots (1)$$

If an equal number of positive and negative mutations (each having the same magnitude of effect) takes place, then the absolute values of the numerator in Formula (1) are the same for a positive and a negative mutation. However, the denominator changes in accordance with the sign of Δv ; the absolute value of ΔQ , therefore, is greater for a negative Δv than for a positive Δv . This means that a lethal gene, even though it shows superviability ($v > 1$) expressed in zygotic viability and is therefore capable of achieving equilibrium, will tend to be eliminated from a population as a result of random spontaneous mutational changes in the lethal-heterozygote-viability-modifying genetic background.

(2.) *Female fecundity* (f) [*or male mating ability* (m)]:—If female lethal heterozygotes have greater fecundities ($f > 1$) than wild-type females, they are maintained in the population (Mukai and Burdick 1959). The zygotic array in the equilibrium population is as follows: $R - 1$ of AA , $2 - R$ of Aa , and none of aa where

$$R = (1 + \sqrt{2(f-0.5)^2 + 0.5})/f$$

If a mutation takes place in the genetic background modifying female fecundity of lethal heterozygotes, the following array will be produced:

Genotype:	$\alpha AA + \beta AA$	αAa	βAa	aa
Fecundity:	1	f	$f + \Delta f$	0
Frequency:	$R - 1$	$(2 - R)(1 - c)$	$(2 - R)c$	0

After one random mating generation, the following zygotic array is produced:

$$(AA) = 1 - Q_1 = \frac{2R^2(R-1)^2 + (R^2-2)(2-R)c\Delta f}{2[R^2(R-1) + (2-R)(1+0.5R)(R^2-2)c\Delta f]}$$

$$(Aa) = Q_1 = \frac{(2-R)[R^2(R-1) + (R^2-2)c\Delta f]}{R^2(R-1) + (2-R)(1+0.5R)(R^2-2)c\Delta f}$$

The change in frequency of lethal heterozygotes (ΔQ) is as follows:

$$\Delta Q = \frac{(2-R) [R^2 (R-1) + (R^2-2) c \Delta f]}{R^2(R-1) + (2-R) (1+0.5R) (R^2-2) c \Delta f} - (2-R)$$

$$= \frac{(2-R) (R^2-2)^2 c \Delta f}{2[R^2(R-1) + (2-R) (1+0.5R) (R^2-2) c \Delta f]} \dots \dots \dots (2)$$

where, when $f > 1$

$$(2-R) = \frac{2(f-1)}{2f-1 + \sqrt{2(f-0.5)^2 + 0.5}} > 0$$

$$\text{and } (R^2-2) = \frac{2}{\sqrt{2(f-0.5)^2 + 0.5} + (f-1)} > 0$$

And, under the same assumptions about mutation as in the case of zygotic viability, the same conclusion can be drawn from Formula (2), *viz.*, the lethal, even though capable of equilibrium, will tend to be eliminated.

In the case of superior mating abilities of males ($m > 1$), the same conclusion can be drawn, other things being equal, because m and f are interchangeable in the above formulae.

(3) *Sperm competitive ability* (s):—If the lethal-carrying sperms show better competitive abilities for fertilization than the lethal-free sperms, namely, $s > 1$, the lethal is maintained in the equilibrium population (MUKAI and BURDICK 1959). The equilibrium zygotic array is as follows: $1/\sqrt{s}$ of AA , $1 - (1/\sqrt{s})$ of Aa , and none of aa .

If a mutation modifying the competitive ability of lethal-carrying sperm takes place in the genetic background, the following array will be produced:

Genotype:	$\alpha AA + \beta AA$	αAa	βAa	aa
Frequency:	$1/\sqrt{s}$	$(1 - 1/\sqrt{s})(1 - c)$	$(1 - 1/\sqrt{s})c$	0

After one random mating generation, the population shows the following zygotic array:

$$(AA) = 1 - Q_1$$

$$= \frac{(\sqrt{s} + 1) \{ \sqrt{s} (1 + s) (1 + \sqrt{s}) + [\sqrt{s} (1 - c) + s + c] \Delta s \}}{s(1 + \sqrt{s})^2 (1 + s) + [(1 + s) (s - c) + 2\sqrt{s}(s + c)] \Delta s}$$

$$(Aa) = Q_1$$

$$= \frac{(\sqrt{s} - 1) \{ (1 + s) \sqrt{s} (1 + \sqrt{s})^2 + [2(s + c) + \sqrt{s}(1 + s)] \Delta s \}}{s(1 + \sqrt{s})^2 (1 + s) + [(1 + s) (s - c) + 2\sqrt{s}(s + c)] \Delta s}$$

The change in frequency of lethal heterozygotes (ΔQ) is as follows:

$$\Delta Q = Q_1 - Q$$

$$= \frac{(\sqrt{s} - 1) (s + 1) c \Delta s}{s \sqrt{s} (1 + s) (1 + \sqrt{s})^2 + \sqrt{s} [(1 + s) (s - c) + 2\sqrt{s}(s + c)] \Delta s} \dots \dots (3)$$

Under the same assumptions about mutation as in the cases of zygotic viability, female fecundity (or male mating ability), we can draw a similar conclusion, *viz.*, the lethal, even though capable of equilibrium by virtue of $s > 1$, will tend to be eliminated.

B. *Drosophila*-type sex chromosomal lethals (XY-type):

1. *Zygotic viability* (v):—It can be shown that, if sex-linked lethal heterozygous females show more than twice the zygotic viability of lethal-free females, namely, $v > 2$, the lethal will reach equilibrium and be maintained in the population. The zygotic array in the equilibrium population is as follows: $1/(v-1)$ of AA , $(v-2)/(v-1)$ of Aa , none of aa , and all males will be AY where Y stands for the Y chromosome.

If a mutation modifying the lethal heterozygote viability takes place in the genetic background, the following array will be produced:

Genotype:	αAA	βAA	αAa	βAa	αAY	βAY
Zygotic						
Viability:	1	1	v	$v + \Delta v$	1	1
Frequency:	$\frac{(1-c)}{(v-1)}$	$\frac{c}{(v-1)}$	$\frac{(v-2)(1-c)}{(v-1)}$	$\frac{(v-2)c}{(v-1)}$	$(1-c)$	c

After one generation of random mating, the following population would be obtained:

$$\begin{aligned}
 (AA) &= 1 - Q_1 = \frac{v}{v(v-1) + (v-2)(2-c)c\Delta v} \\
 (Aa) &= Q_1 = \frac{(v-2)[v + (2-c)c\Delta v]}{v(v-1) + (v-2)(2-c)c\Delta v} \\
 \Delta Q &= Q_1 - Q = \frac{(v-2)(2-c)c\Delta v}{(v-1)[v(v-1) + (v-2)(2-c)c\Delta v]} \dots\dots\dots (4)
 \end{aligned}$$

The form of Formula (4) is the same as those given before, (1), (2), and (3), *viz.*,

$$\Delta Q = \frac{k_1 \Delta x}{k_2 + k_3 \Delta x}$$

where k_i is a positive function of the viability parameters (v , f , m or s) and the frequency of mutation (c), and Δx is the viability change magnitude associated with mutation in the genetic background. The lethal in this case, therefore, will tend also to be eliminated from the population.

2. *Female fecundity* (f):—The requirement for lethal equilibrium is $f > 2$. The equilibrium zygotic array is $f/[2(f-1)]$ of AA , $(f-2)/[2(f-1)]$ of Aa , none of aa , and all males AY . After a heterozygote-modifying mutation has taken place, the female array will be:

Genotype:	$\alpha AA + \beta AA$	αAa	βAa
Fecundity:	1	f	$f + \Delta f$
Frequency:	$\frac{f}{2(f-1)}$	$\frac{(f-2)(1-c)}{2(f-1)}$	$\frac{(f-2)c}{2(f-1)}$

One generation of random mating will produce

$$\begin{aligned}(AA) &= 1 - Q_1 = \frac{f^2 + (f-2) c \Delta f}{2[f(f-1) + (f-2) c \Delta f]} \\(Aa) &= Q_1 = \frac{(f-2)(f+c \Delta f)}{2[f(f-1) + (f-2) c \Delta f]} \\ \Delta Q &= Q_1 - Q = \frac{(f-2) c \Delta f}{2(f-1)[f(f-1) + (f-2) c \Delta f]} \dots\dots\dots (5)\end{aligned}$$

Formula (5) has the same form as those shown previously.

The male viability parameters, m and s , are not involved since sex-linked lethals will not exist in males.

C. Chicken-type sex chromosomal lethals (ZW-type):

The following general relationship of the pertinent parameters in the equilibrium population can be shown for the case where the lethal is sex-linked in a species with heterogametic females under the condition of $1 + s < smv$:

$$Q = \frac{1 + s - smv}{1 + s - smv - m} \dots\dots\dots (6)$$

Formula (6) can be used to show that: (1) high values of s will not keep a lethal in a population, (2) m and v , while capable of equilibrium-generating values, are subject to the same type of ΔQ relationship as has been shown for f and v in the case of sex-linked lethals in the XY system.

All of the above formulae lead to the same conclusion with regard to the destiny of a recessive lethal in a random mating population: Random mutations in the lethal-heterozygote-viability-modifying background will tend to eliminate the lethal from the population even though the lethal heterozygote has a viability parameter sufficiently high to produce equilibrium. This will be true if the background mutations are equally likely to be positive or negative modifiers and if the absolute magnitude of the different mutations is the same.

EXPERIMENTAL RESULTS

MUKAI and BURDICK (1959) established four artificial autosomal lethal heterozygous populations involving the second chromosome recessive lethal $l(2)55i$ in *Drosophila melanogaster*. In Population 1 which had high homozygosity in the genetic background, and in Population 2 which had high heterozygosity in the starting generation, both of which started with a frequency of lethal heterozygotes, $Q_1 = 1$, lethal heterozygotes reached equilibrium in the seventh generation with average frequencies of $Q = 0.42$. In Population 3 which had genetic background derived from Population 1, and in Population 4 with the genetic background of Population 2, the frequencies of the lethal started at $Q_1 = 0.05$ and increased to about the same values obtained for the first two populations. After 30–60 generations, SCHNICK, MUKAI, and BURDICK (1960) again estimated the frequencies of lethal heterozygotes in the above mentioned artificial populations.

The combined results of these two papers are recalculated and summarized in Table 1 and graphically presented in Figure 1 ($Q_n = \frac{2}{1+n}$ is the expected frequency if the viability of $l/+$ is the same as $+/+$). The results in the bottles of each generation are pooled for the sake of convenience, although there are heterogeneities between subpopulations within generations in Population 2 (generation 46–50) and Population 4 (generation 27–31). Populations 2 and 4 consist of seven and ten subpopulations, respectively, cultured in different milk bottles.

FIGURE 1.—Frequency of $l(2)55i$ heterozygotes in various populations compared with the expected frequency, $Q_n = 2/[1+n]$.

TABLE 1

Temporary equilibrium frequencies in various $l(2)55i$ heterozygous populations

Generation	Population 1	Population 2	Population 3	Population 4
Q_7-Q_{16}	0.420 ± 0.019	0.424 ± 0.017	$0.326 \pm 0.032^*$	$0.423 \pm 0.030^*$
$Q_{27}-Q_{31}$				0.337 ± 0.025
$Q_{33}-Q_{37}$			0.220 ± 0.034	
$Q_{46}-Q_{50}$		0.305 ± 0.031		
$Q_{57}-Q_{61}$	0.193 ± 0.011			
Q_{72}	$0.159 \pm 0.055^\dagger$			

* Frequency estimated in the 15th generation only.

† This was estimated from a population which had been held in a large cage, and which had been established from generation 64 of population 1. The generation, 72, is an estimate based upon a 15-day life cycle.

In each population the frequencies of lethal heterozygotes have decreased significantly with generations. The temporary equilibrium values from the seventh to the 16th generation are 0.420 and 0.424 in Populations 1 and 2, respectively. The frequency of lethal heterozygotes dropped to 0.193 (generation 57–61), to 0.159 (estimated generation 72) in Population 1 and to 0.305 (generation 46–50) in Population 2. Although there are different genetic backgrounds in Populations 1 and 2, they are comparable because they have almost the same temporary equilibrium frequency during the period generation 7–16. The frequency of lethal heterozygotes from the 57th to 61st generation ($Q = 0.193$) in Population 1 is significantly smaller than that from the 46th to the 50th generation ($Q = 0.305$) in Population 2 [$\chi^2_{d.f. = 1} = 14.11$ ($p < 0.0005$) by the 2×2 contingency table method].

In the early generations of Populations 3 and 4, only the frequencies in generations 10 and 15 were estimated. The result in the 15th generation, therefore, is not a good estimate of the temporary equilibrium frequency in these populations if the effect of genetic drift is taken into consideration. However, these are the best estimates we have for the early generations of these populations. The mean frequencies of lethal heterozygotes from generation 33 to generation 37 in Population 3, and those from generation 27 to generation 31 in Population 4 dropped significantly. In Population 3, $\chi^2_{d.f. = 1} = 9.13$ ($0.005 > p > 0.001$). In Population 4, $\chi^2_{d.f. = 1} = 6.37$ ($0.025 > p > 0.01$). It should be stressed that the results of Population 4 show a smaller χ^2 value than those of Population 3, probably because the frequencies of lethal heterozygotes in Population 4 were estimated in earlier generations (generation 27–30).

The demonstrated gradual decline of lethal frequency in these four populations is to be expected on the basis of the lethal-heterozygote-viability-modifying mutation hypothesis, previously described.

Lethal genes and population productivity

In general, population size will be relatively stable in a closed environment. A population containing a heterotic lethal will have the lethal at equilibrium frequency, although the reproductive potential of the population might not be at the maximum value. If such a population should suddenly expand to infinite size, the reproductive potential would govern the rate at which it would expand. We have chosen to call the reproductive potential, population productivity (P), and to define it as the potential offspring of the population. The relative ability of different populations to evolve, or expand, is partly a function of P , and therefore P is a component of the adaptive value of a population. Obviously the value of P is a function of gene frequency and the magnitude of the lethal heterozygote viability parameter. In the following models we consider that P is unity in the homozygous wild-type population and that only one viability parameter at a time is varying.

A. Autosomal lethals:

(1.) *Zygotic viability* (v):—In the case where v varies, population productivity can be expressed as:

$$P = \frac{1}{4} \left\{ (1 - 2v) \left[Q - \frac{2(v-1)}{2v-1} \right]^2 + \frac{4v^2}{2v-1} \right\} \dots\dots\dots (7)$$

This formula indicates that P is maximum when $Q = \frac{2(v-1)}{2v-1}$ and that P will be greater than one at certain values of Q if v is greater than one. $Q = \frac{2(v-1)}{2v-1}$ also happens to be the equilibrium frequency of lethal heterozygotes where $v > 1$ (the minimum for maintenance of a lethal in a population) which means that population productivity will be at a maximum when the population is in equilibrium. The relationships between Q , v , and P are graphically shown in Figure 2.

(2.) *Female fecundity* (f):—Where f varies, population productivity is

$$P = 1 + \frac{(f-1)^2}{f} - \frac{f}{4} \left[Q - \frac{2(f-1)}{f} \right]^2 \dots\dots\dots (8)$$

and P maximum is obtained when $Q = \frac{2(f-1)}{f}$ which is always larger than $Q = 2 - [1 + \sqrt{2(f-0.5)^2 + 0.5}]/f$, the equilibrium frequency of lethal heterozygotes. Figure 3 shows P as a function of f and Q .

(3.) *Male mating ability* (m):—Population productivity is

$$P = 1 - \frac{mQ^2}{4(1-Q+mQ)} \dots\dots\dots (9)$$

FIGURE 2.—Relationship between P and Q for autosomal lethals with various values of v .

FIGURE 3.—Relationship between P and Q for autosomal lethals with various values of f .

We can see that,

$$\frac{mQ^2}{4(1 - Q + mQ)} > 0$$

and, therefore, high m values of lethal heterozygotes would not increase population productivity.

(4.) *Sperm competitive ability* (s):—If l -carrying and wild-type sperm are considered to have varying competitive abilities in effecting fertilization, population productivity can be expressed as follows:

$$P = 1 - \frac{sQ}{2(1 + s)} \dots \dots \dots (10)$$

Since

$$\frac{sQ}{2(1 + s)} > 0$$

we can conclude that l -carrying sperm always decrease population productivity whether or not they have greater-than-one competitive ability.

B. Sex chromosomal lethals, *Drosophila* type (XY):

(1.) *Zygotic viability* (v):—We consider that a sex-linked lethal will not exist in males under the XY sex chromosome system. Therefore, zygotic viability differences between lethal heterozygotes and homozygous wild types will be found only in females; homozygous wild-type males and females have equal viability. Population productivity in terms of v can be expressed as

$$P = 1 - \frac{Q(2 - v)}{4} \dots \dots \dots (11)$$

When v is larger than 2, P will be greater than one; as v increases above 2, P increases monotonically which is a contrast to the maximum for P (function of v) for autosomal lethals. The minimum v for maintenance of a sex-linked lethal in a population is also 2.

(2.) *Female fecundity* (f):—When f varies, population productivity can be expressed as

$$P = 1 - \frac{(4 - 3f)Q}{4} \dots\dots\dots (12)$$

which indicates that P becomes larger than one, increasing monotonically, compared with the wild-type population, when $f > 4/3$.

Male mating ability and sperm competitive ability are not involved in sex-linked lethal viability since such lethals will not exist in males under the XY sex chromosome system.

C. Sex chromosomal lethals, chicken type (ZW):

(1.) *Zygotic viability* (v):—Population productivity in terms of v under the ZW sex chromosome system is exactly the same as under the XY system [Formula (11)].

(2.) *Female fecundity* (f):—Female fecundity is not considered because it is assumed that females will not carry lethals under the ZW system.

(3.) *Male mating ability* (m):—When m varies, P becomes

$$P = 1 - \frac{mQ^2}{4(1 - Q + mQ)}$$

which is exactly the same as Formula (9). It is clear that high values of m cannot increase population productivity.

(4.) *Sperm competitive ability* (s):—Population productivity in terms of s under the ZW sex chromosome system can be expressed by the same formula, (10), as that derived for s for autosomal lethals. The same conclusion, that lethal heterozygote heterosis cannot work through s to increase population productivity, is appropriate.

DISCUSSION

We have shown experimentally and theoretically that heterozygotes of $l(2)55i$ are heterotic and capable of attaining equilibrium in two different genetic backgrounds (MUKAI and BURDICK 1959) and that the superviability of these heterozygotes is ultimately attributable to higher female fecundity (f) (SCHNICK, MUKAI and BURDICK 1960). In the present paper we are concerned about the effect of random mutational changes in the lethal-heterozygote-viability-modifying genetic background on equilibrium levels of superviable lethals. We find that random mutations in the background (each mutation with the same absolute magnitude of effect and equally likely to be a positive or a negative modifier) will tend to eliminate the lethal from the population even though the heterozygote has a viability parameter (m , v , f , or s) sufficiently high to produce stable equi-

librium. This expectation is born out in our later generation data on *l(2)55i* in which the frequency has been noted to decline from the original, apparently stable, equilibrium levels. Since all of the lethal situations (i.e., autosomal, sex-linked XY, sex-linked ZW) and each of the viability parameters give the same expectation in our theoretical examination, we are led to expect that no lethal will continue to exist indefinitely in a population unless new modifying mutations are continually more favorable than unfavorable for heterozygote viability (inversion and balanced lethal systems would maintain a lethal but we have extended our examination only to systems in which normal recombination takes place).

We have examined the question of whether lethals can be "adaptive" and contribute to the over-all fitness of a population. We find that under some circumstances, notably the one obtaining for *l(2)55i*, they are adaptive and favored by natural selection. The relative potential offspring of a population has been called population productivity (P). We have shown that, within a certain range of gene frequency, heterotic lethals increase P if they operate through the viability parameters v or f for autosomal or XY system sex-linked lethals or through v for ZW system sex-linked lethals. Heterotic lethals that operate through m or s , although capable of equilibrium, can only serve to reduce P , and the amount of reduction in P is related to the degree of heterosis.

For autosomal lethals, v or f need only be greater than unity to produce equilibrium but, for sex-linked lethals of either system, v must be greater than two, and f , which can only operate in the XY system, must be also greater than two to produce equilibrium. So, if heterotic lethals are found in populations, it is to be expected that they would be autosomal and operate through v or f . These considerations indicate the essential differences in the genetic systems governing autosomal and sex-linked lethals and are adequate reason for not extending generalizations from one type of lethal to another.

Random mating populations such as *Drosophila melanogaster* go through cycles of expansion and contraction where P is important. Therefore, if we find heterotic lethals in *Drosophila*, it seems more likely that they would operate through v or f since such lethals, for a given amount of associated heterosis, have a greater amount of reproductive potential under conditions of oscillating population size than those that operate through m or s . Our second chromosome lethal, *l(2)55i*, has been shown to operate at first probably through m and f and later only through f so that its existence in a wild population and its mode of action are to be anticipated from theoretical considerations.

The equilibrium level of lethal heterozygote frequency of an autosomal heterotic lethal that operates through f has been shown to be less than the level that produces maximum population productivity. This means that, during periods of population expansion, the lethal frequency might increase.

Our particular lethal, *l(2)55i*, is beneficial to individuals that carry it and to populations that contain it; other lethals of similar action might be found. But, the specifications for such lethals restrict them largely to the autosomes and call for action through v or f . Not every lethal is even potentially beneficial, and those

that are must act in only a certain way. On the other hand, this denies that all lethals are potentially harmful to populations and requires that the v and f values be known before the lethal effect can be assessed.

Finally, it must be said that even though a lethal is both capable of equilibrium and effective in increasing population productivity, ultimately it probably will be lost from the population as a result of "mutational static" in the lethal-heterozygote-viability-modifying background. The "beneficial lethal" effect of any given lethal, therefore, is likely to be transitory—the lethal might occur as a mutation, increase to its equilibrium level improving population productivity as it increases, and then slowly decline. The population might be better off for having had such a lethal, but, if so, the effect was that of a temporary stimulant. The frequency of this kind of lethal mutation is unknown—one has definitely been found in a wild population and described in this series of papers. But, if the frequency is even a small part of the total lethal mutation burden, the "beneficial lethal" effect might be a repeated experience of the population and an important attribute of its evolution.

SUMMARY

Random mutations tend to eliminate $l(2)55i$ from a population even though the heterozygote has a viability parameter sufficiently high to produce stable equilibrium.

Theoretical considerations regarding other autosomal and sex-linked lethals are given.

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