HETEROZYGOUS EFFECTS AND FREQUENCY CHANGES OF LETHAL GENES IN POPULATIONS¹

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IN recent years several experiments have been conducted on the frequency changes of lethal genes or lethal-bearing chromosomes in populations with or without altering mutations rates. There appears, however, to be no appropriate mathematical theory for analyzing the experimental data, and the conclusions reached by various authors are not necessarily consistent with each other (WALLACE 1956, 1962; DYER 1966; TOBARI and MURATA 1968). In the following I shall develop some mathematical formulae applicable to such data and discuss the heterozygous effect of lethal genes, using available *Drosophila* data. The equilibrium frequency of lethal genes in finite populations will also be considered.

CHANGE IN THE FREQUENCY OF LETHAL GENES

Partially recessive lethals: Consider a randomly mating population of size N , in which a lethal gene a and its allelic normal gene A are segregating. Let the frequency of a be q and the fitnesses of the three possible genotypes AA , Aa , and aa be 1, $1 - h$, and $1 - s$, respectively, where s is 1 for a completely lethal gene and $0.5 < s < 1$ for a semilethal gene. In general, the stochastic change of gene frequency in a finite population is expressed by the following FOKKER-PLANCK equation

$$\frac{\partial \phi}{\partial t} = \frac{1}{2} \frac{\partial^2}{\partial q^2} (V_{\delta q} \phi) - \frac{\partial}{\partial q} (M_{\delta q} \phi) \quad (1)$$

where $\phi = \phi(q, t)$ is the frequency distribution of q at time t , and $M_{\delta q}$ and $V_{\delta q}$ are the mean and the variance of the change of gene frequency per generation (see KIMURA 1964). In the present case $M_{\delta q} = (1 - q)u - \{h + (s - 2h)q\}q(1 - q)$ and $V_{\delta q} = q(1 - q)/(2N)$, where u is the mutation rate from A to a , the reverse mutation being assumed to be negligible. At a given locus, the frequency of the lethal gene, q , is generally very small, unless it is raised artificially. Thus, if h is much larger than $\sqrt{us}$ and N is sufficiently large ($4Nh \gg 1$), $M_{\delta q}$ can be approximated by $u - hq$ or $h(\tilde{q} - q)$, where $\tilde{q} = u/h$, neglecting the second and higher order terms of q . The mean change of gene frequency is then linear with respect to q .

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A complete solution of (1) under linear pressure has been given by GOLDBERG (1950) and KIMURA (CROW and KIMURA 1956). KIMURA has also obtained the n th moments of the distribution $\phi(q, t)$ about the origin in the t th generation. In the present case it becomes

$$\mu'_{n(t)} = \sum_{i=0}^{\infty} \binom{n}{i} \frac{\Gamma(B+n)\Gamma(A+2i)\Gamma(A-B+i)\Gamma(A+i-1)}{\Gamma(A+n+i)\Gamma(B+i)\Gamma(A-B)\Gamma(A+2i-1)} F(A+i-1, -i, A-B, 1-q_0) \exp \left[-i \left(h + \frac{i-1}{4N} \right) t \right] \quad (2)$$

where $A = 4Nh$, $B = 4Nu$, and $F(\cdot, \cdot, \cdot, \cdot)$ is the hypergeometric function, q_0 being the initial gene frequency at $t = 0$. From the above formula we can obtain the mean and variance of q in the t th generation. The mean is

$$\bar{q}^t = \bar{q} + (q_0 - \bar{q})e^{-ht} \quad (3)$$

and, if $2Nh \gg 1$, the variance approximates to

$$\sigma_t^2 = \bar{\sigma}^2 + \frac{(q_0 - \bar{q})}{2Nh} e^{-ht} - (q_0 - \bar{q})^2 e^{-2ht} + \left\{ \sigma_0^2 + \bar{\sigma}^2 + (q_0 - \bar{q})^2 - \frac{q_0}{2Nh} \right\} e^{-[2h + 1/(2N)]t} \quad (4)$$

where σ_0^2 and $\bar{\sigma}^2 (= \bar{q}/(4Nh))$ are the initial and equilibrium values of the variance of gene frequency, respectively. When $t = \infty$, the mean and variance become identical to those of the stationary distribution of q given by NEI (1968). The change of the mean gene frequency when $q_0 = 0$, $u = 10^{-5}$, and $h = 0.03$ is given in Figure 1.

In most cases the quantity experimentally determined is not the frequency of individual lethal genes but the frequency of lethal-bearing chromosomes in a population. The frequency of lethal chromosomes (Q) is not a simple sum of

FIGURE 1.—Accumulation of lethal genes due to mutation in large populations. For overdominant genes s_1 is assumed to be 0.01, while the value of h for partially recessive genes is 0.03. The mutation rate is assumed to be 10^{-5} for all three kinds of lethals. The curve for partially recessive lethals holds true also in relatively small populations ($4Nh \gg 1$).

lethal gene frequencies at the individual loci. However, if lethal genes are randomly distributed on chromosomes, the transformation $Q_i = -\log_e(1 - Q)$ gives an estimate of $\sum_{i=1}^n q_i$, where n is the number of loci in which lethal genes may occur and i refers to the i th locus. Therefore, the mean ($\bar{Q}_1$) of Q_1 in the t th generation is given by

$$\bar{Q}_{1(t)} = \tilde{Q}_1 + (Q_{1(0)} - \tilde{Q}_1)e^{-ht} \quad (5)$$

where $\tilde{Q}_1$ is $\sum_{i=1}^n \tilde{q}_i$, and h is assumed to be the same for all loci. On the other hand, the variance of Q_1 is given by $\Sigma \sigma_i^2$. Thus, if $Q_{1(0)} = \tilde{Q}_1$, the variance (V_t) of Q_1 in the t th generation becomes

$$V_t = \tilde{V} + (V_0 - \tilde{V})e^{-[2h + 1/(2N)]t} \quad (6)$$

where $\tilde{V} (= \tilde{Q}_1/4(Nh))$ is the variance at $t = \infty$ (see NEI 1968).

Completely recessive lethals: It is not easy to solve equation (1) for $h = 0$, and I have been unable to obtain any formulae for the changes in mean and variance of lethal gene frequency except for large populations. In large populations, where the variance of gene frequency is negligible, the change of q per generation is approximately given by

$$\frac{dq}{dt} = u - sq^2$$

Solution of this gives

$$q_t = \begin{cases} \tilde{q} \tanh(c_1 + \sqrt{su}t) & q_0 < \tilde{q} \\ \tilde{q} \coth(c_2 + \sqrt{su}t) & q_0 > \tilde{q} \end{cases} \quad (7)$$

where $\tilde{q} = \sqrt{u/s}$ (equilibrium frequency), $c_1 = \operatorname{arctanh}(q_0/\tilde{q})$, and $c_2 = \operatorname{arccoth}(q_0/\tilde{q})$. The temporal change of q_t for $q_0 = 0$, $s = 1$, and $u = 10^{-5}$ is given in Figure 1. It is seen from this figure that in early generations the gene frequency increases almost linearly, but the rate of increase is gradually reduced in later generations. It takes a long time for the gene frequency to reach the equilibrium value compared with the case of partially recessive lethals. If q_0 is 0 for all the lethal loci, $Q_{1(t)}$ becomes

$$Q_{1(t)} = \tilde{Q}_1 \tanh \sqrt{su}t \quad (8)$$

where $\tilde{Q}_1 = n\sqrt{u/s}$, assuming that u and $s > 0.5$ are the same for all the loci.

In small populations the random fluctuation of gene frequencies becomes important, and the change in mean gene frequency depends on population size as well as on u and s . It is not clear how it depends theoretically, but the mean gene frequency is expected to be always smaller than that in large populations. MILLER (1962) has worked out an asymptotic formula for the smallest eigenvalue of equation (1) for the case of completely recessive genes with no mutation (see also ROBERTSON 1962). In our notations it becomes $3\sqrt{s}/(8\sqrt{N})$. This indicates that the rate of loss of completely recessive lethal genes is much larger than that of neutral genes ($1/(2N)$). With $t \rightarrow \infty$, the gene frequency reaches the equi-

librium value, which also depends on population size and is smaller in small populations than in large populations (see Figure 4).

With the aim of obtaining an idea about the change of gene frequency in small populations, Monte Carlo simulations were conducted, using an IBM 360 computer. In this experiment $N = 200$ and $s = 1$ were adopted. A rather high mutation rate—i.e., $u = 0.0025$, was used in order to save computer time. From these parameters the equilibrium gene frequency is expected to be 0.043 from formula (10). Selection and mutation were assumed to occur deterministically, the expected gene frequency in the next generation being given by $q' = q(1-q)/(1-q^2) + u(1-q)$ approximately, where q is the gene frequency in the preceding generation. From the gamete pool with gene frequency q' , 400 gametes were randomly chosen to form the next generation by using pseudo-random numbers. Starting from $q_0 = 0$, the changes of gene frequency during the first 80 generations were examined with 50 replicate runs. The result of this experiment indicated that the gene frequency shows a large random fluctuation after the population has reached equilibrium. Thus, a similar simulation was again conducted, now examining the changes of gene frequency for the first 100 generations with 50 replicate runs. In this simulation a completely different set of pseudo-random numbers was used.

The results of these simulations are given in Figures 2 and 3. It is clear from Figure 2 that the rate of increase in gene frequency in early generations is very close to that of large populations—i.e., the curve given by formula (7). However, the rate of increase is gradually reduced in later generations, and the mean gene frequency becomes lower than that for large populations. Thus, when one wants to study the heterozygous effect of lethal genes through the frequency changes

FIGURE 2.—Changes of the mean frequency of completely recessive lethal genes (average of 50 replications) in Monte Carlo simulations. The population size is 200 and the mutation rate is 0.0025. The broken and dotted lines are the results of the first and second simulations, respectively. The solid line represents the theoretical curve for large populations ($N = \infty$).

FIGURE 3.—Distributions of frequencies of completely recessive lethal genes in various generations in Monte Carlo simulations. The population size is 200 and the mutation rate is 0.0025. The distribution for generations 51-60 represents the stationary distribution.

in relatively small populations, it is desirable to use data from early generations rather than data obtained from later generations. Figure 2 suggests that the gene frequency has reached the equilibrium state by the 40th generation. The equilibrium mean gene frequency, therefore, can be estimated from the values for the 41st and later generations. It becomes 0.044, which is very close to the expected value—i.e., 0.043. It is observed that the random fluctuation of the mean gene frequency for 50 replications is very small in early generations, but also that it becomes large in later generations, particularly in the neighborhood of equilibrium. The distributions of gene frequency for various generations are given in Figure 3.

Overdominant lethals: Let the fitnesses of AA , Aa , and aa be $1-s_1$, 1, and 0,

respectively. If s_1 is small, the change of q per generation in a large population is approximately given by

$$\frac{dq}{dt} = (1+s_1)q(1-q)(\hat{q}-q) + (1-q)u$$

$$\approx (1+s_1)q(\hat{q}-q) + u$$

where $\hat{q} = s_1/(1+s_1)$ and q is assumed not to be much larger than $\hat{q}$. Solution of the above formula gives

$$q_t = \begin{cases} \frac{1}{2} \hat{q} - \frac{a}{2} \tanh \left(c_1 - \frac{a}{2} (1+s_1)t \right) & q_0 \leq \bar{q} \\ \frac{1}{2} \hat{q} - \frac{a}{2} \coth \left(c_2 - \frac{a}{2} (1+s_1)t \right) & q_0 \geq \bar{q} \end{cases} \quad (9)$$

where $a = [\hat{q}^2 + 4u/(1+s_1)]^{1/2}$, $\bar{q} = (\hat{q}+a)/2$ (equilibrium frequency), $c_1 = \operatorname{arctanh} (\hat{q}-2q_0)/a$, and $c_2 = \operatorname{arccoth} (\hat{q}-2q_0)/a$. A typical form of the change of q_t is given in Figure 1, where $q_0 = 0$, $s_1 = 0.01$, and $u = 10^{-5}$ are assumed. The gene frequency increases logistically in this case, which sharply contrasts with the frequency changes of partially recessive or completely recessive lethals. Thus, in large populations it is possible to distinguish the three types of lethals in terms of the pattern of accumulation of lethals due to mutation in populations.

In small populations, however, the random fluctuation of gene frequencies becomes important, and the mean gene frequency is expected to be smaller than the value given by (9), as in the case of completely recessive lethals (see MILLER, 1962). Thus, the differences among the frequency changes of the three different types of lethals are less pronounced in small populations.

MEAN GENE FREQUENCY IN FINITE EQUILIBRIUM POPULATIONS

A slight positive or negative effect of lethal genes in the heterozygotes also gives a profound effect on the equilibrium gene frequency in populations. WRIGHT (1937) showed that the mean gene frequency of completely recessive lethals with $s = 1$ in a population of size N is given by

$$\bar{q} = \Gamma(2Nu+1/2)/(\sqrt{2N} \Gamma(2Nu)) \quad (10)$$

which is approximately equal to $u\sqrt{2\pi N}$ if $2Nu$ is equal to or smaller than 0.01. For semilethal genes, $\sqrt{2N}$ in (10) is replaced by $\sqrt{2Ns}$ (NEI 1968). On the other hand, NEI (1968) showed that if h is much larger than $\sqrt{su}$ and $2N(s-2h)q^2$ is negligibly small compared with $4Nhq$ (or roughly $4Nh \gg 1$), the mean gene frequency is approximately given by

$$\bar{q} = u/h \quad (11)$$

which is independent of population size. When $4Nh$ is not large, numerical integrations are required for obtaining $\bar{q}$, using WRIGHT's (1937) formula for gene frequency distribution. It is not easy to obtain a general formula for overdominant lethals, but if population size is small ($4Nu \ll 1$) and s_1 is smaller than 0.01, the mean gene frequency is approximately given by

$$\bar{q} = 2u\sqrt{(2\pi N)/(1+s_1)} [\operatorname{erf}((1-\hat{q})\sqrt{4S}) + \operatorname{erf}(\hat{q}\sqrt{4S})] e^{2S\hat{q}^2} \quad (12)$$

FIGURE 4.—Mean gene frequencies in equilibrium populations. For overdominant genes s_1 is assumed to be 0.01, while the value of h for partially recessive genes is 0.03. The mutation rate is assumed to be 10^{-5} for all three kinds of lethals.

where $S = N(1+s_1)$ and $\text{erf}(x) = \int_0^x (2\pi)^{-1/2} e^{-t^2/2} dt$.

ROBERTSON (1962) has obtained a similar formula for the mean frequency of heterozygotes for overdominant nonlethal genes. When N is relatively large and s_1 is not small, numerical computations are required for obtaining $\bar{q}$.

Figure 4 shows the mean gene frequencies in populations of various sizes for the three different kinds of lethals with $s = 1$. For partially recessive lethals $h = 0.03$ is assumed, while the value of s_1 for overdominant genes is 0.01. The mutation rate is 10^{-5} for all the three cases. Figure 4 shows that the frequency for partially recessive lethals is independent of population size except in very small populations, while the frequency of completely recessive and of overdominant lethals increases as population size increases. In large populations the equilibrium frequency of lethal genes is profoundly affected by a slight positive or negative effect of the genes in the heterozygotes. These properties may also be used for the study of heterozygous effects of lethal genes.

DISCUSSION

From these studies it is clear that the frequency change and equilibrium frequency of lethal genes in large populations are highly dependent on the heterozygous effects of the genes. In small populations, however, the differences in gene frequency are less pronounced. Thus, it is very important to know the effective population size when studying the heterozygous effects of lethal genes by examining frequency changes or equilibrium frequencies.

WALLACE (1956; see also WALLACE and KING 1951) conducted an extensive

experiment on the accumulation of lethal genes on the second chromosome of *Drosophila melanogaster* under chronic irradiation with γ rays. His data on the lethal chromosome frequencies up to the 81 st generation in population 5 and the 80 th generation in population 6 were analyzed by PROUT (1954). The size of population 5 was frequently fewer than 1,000 individuals, while the size of population 6 was about 10,000. PROUT fitted the equation $Q_t = \bar{Q}(1 - e^{-kt})$ to the frequencies of lethal chromosomes without logarithmic transformations, where $\bar{Q}$ is the equilibrium frequency of lethal chromosomes. Thus, his constant k does not permit simple genetic interpretations. His least-squares estimate of $\bar{Q}$ was 0.857 in population 5 and 0.865 in population 6, the difference not being statistically significant. The data for the later generations given in Figure 5 in WALLACE's (1956) paper indicate that these estimates are roughly correct. The fact that the equilibrium frequency is nearly the same for the two populations despite the large difference in population size suggests that most of the lethal genes are partially recessive. Thus, equation (5) was fitted to the same data, using method (1) given in the APPENDIX to this paper. In the estimation of h , $\bar{Q}_1$ was obtained by transforming PROUT's estimate of $\bar{Q}$, and the data from the first 46 generations were used. No weighting was made for the value of y in the APPENDIX, since the number of chromosomes examined for each generation was not given. The estimates of h obtained for populations 5 and 6 are 0.021 and 0.023, respectively. These are close to PROUT's estimates obtained from an analysis of the equilibrium chromosome frequencies. The fit of the equation to the observations

FIGURE 5.—Frequency changes of lethal second chromosomes in *Drosophila melanogaster* under irradiation (data of WALLACE). The curvilinear lines represent the expected changes of chromosome frequencies.

is quite satisfactory in view of a rather large variance of Q_1 , most of which is due to random genetic drift (Figure 5).

WALLACE (1956) also examined the accumulation of lethals due to spontaneous mutation. His result (Figure 5 *ibid.*) shows that the frequency of lethal chromosomes reaches the equilibrium value in about 80 generations as in the case of irradiated populations. This is a strong indication of partial recessiveness of lethal genes. If they were completely recessive or overdominant, it would take a much longer time for the frequency of lethals to reach the equilibrium value in view of the mutation rate per locus of the order of 10^{-5} (see Figure 1).

TOBARI and MURATA (1968) conducted a similar experiment with a population (2,000 individuals) of *Drosophila melanogaster*, applying a high dose of acute X rays (sperm irradiation). Using a method similar to method (2) in the APPENDIX, they estimated h to be 0.073. This rather high estimate perhaps reflects that the rate of induction of chromosome aberrations such as translocations was higher in this experiment than in WALLACE's because of both a higher dose of radiation applied and sperm irradiation. DYER's (1966) experiment, though similar in type, was conducted with an extremely small population—i.e., 50 individuals, so that equation (5) is not necessarily applicable. However, if we estimate h from his data for the first 12 generations, where the variance of Q_1 is expected to be small, by using method (3) in the APPENDIX, it becomes 0.069. ($n_{(t)}$ was assumed to be 100 for all generations; DYER 1966). This value could be an overestimate because of both small population size used and sperm irradiation, but it is not incompatible with the view that lethal genes are slightly deleterious on the average.

WALLACE (1956) derived two subpopulations (populations 17 and 18) from his population 5 and one (population 19) from his population 6 and examined the decline of lethal chromosome frequencies after cessation of irradiation. He noted an extremely slow rate of decline in population 19 during the first 24 generations. Figure 5 in his paper suggests that the equilibrium frequency of lethal chromosomes in nonirradiated populations (his populations 1 and 3) is about 20%. Thus, using this value and the lethal chromosome frequencies for various generations given in his Table 3, we can estimate the heterozygous effect of lethal genes, although the fluctuation of lethal chromosome frequencies is extremely large. The unweighted estimate of h becomes 0.024 in population 19. It is in good agreement with the values estimated from populations 5 and 6. The estimates of h in populations 17 and 18 are 0.073 and 0.108, respectively. These values are considerably larger than the previous estimates. Note, however, that the variance of gene or chromosome frequencies is expected to be much larger when they decrease than when they increase. Therefore, in estimating h from a curve of decline in lethal chromosome frequency, it is necessary to set up several replications.

All the data on frequency changes of lethal chromosomes analyzed above indicate that lethal genes are on the average slightly deleterious in the heterozy-

gous condition. Of course, this does not mean that there are no completely recessive lethals or overdominant lethals. It seems, however, that the proportion of overdominant lethals is small, since they have a much larger effect on the frequency changes of lethal chromosomes than partially recessive lethals. This conclusion is consistent with that reached from analyses of the equilibrium frequencies in populations (CROW and TEMIN 1964; NEI 1968). On the other hand, the results of viability tests of lethal heterozygotes do not necessarily agree with this conclusion. Examining the viability of heterozygotes for lethal and semilethal chromosomes extracted from the same populations as analyzed here (populations 5, 6, 17, 18, 19) and some others, WALLACE (1962) reported that shortly after irradiation started, lethal genes showed a deleterious effect on heterozygote viability but later developed an enhancing effect on viability—i.e., an overdominant effect. This disagreement between the two sorts of data could only be accounted for by assuming that there is a negative correlation between viability and fertility and the total fitness of lethal heterozygotes is slightly lowered compared with that of lethal-free homozygotes in this case.

SUMMARY

Mathematical formulae for the frequency changes of lethal genes or lethal-bearing chromosomes in populations are developed, taking into account the heterozygous effect of lethal genes. The relation between the equilibrium mean gene frequency and population size is also studied. Analyses of *Drosophila* data on the frequency changes of lethal chromosomes due to mutation and selection have indicated that lethal genes are, on the average, slightly deleterious in heterozygous condition.

APPENDIX

METHODS FOR ESTIMATING THE HETEROZYGOUS EFFECT OF PARTIALLY RECESSIVE LETHAL GENES

In the following we assume that $h \gg \sqrt{su}$ and $4Nh \gg 1$, so that formula (5) is applicable. We also assume that Q_1 is estimated from a large population or from replicated small populations, so that the variance of Q_1 is small.

(1) If Q_1 is known, h can be estimated as follows:

From formula (5) we have

$$y = -\log_e \frac{\bar{Q}_1 - Q_{1(t)}}{\bar{Q}_1 - Q_{1(0)}} = ht$$

where $Q_{1(t)} = \bar{Q}_{1(t)}$. Therefore, the estimate of h is

$$\hat{h} = \Sigma wy / \Sigma wt^2$$

where w is the weight for y and given by the reciprocal of the variance of y . The variance of y is approximately given by

$$V_y = \frac{Q_{(t)}}{(\bar{Q}_1 - Q_{1(t)})^2 (1 - Q_{(t)})n_{(t)}}$$

where $n_{(t)}$ and $Q_{(t)}$ are the number of chromosomes examined and the frequency of lethal chromosomes in the t th generation, respectively. In this case $Q_{1(t)}$ should be less than $\bar{Q}_1$. Thus, the use of early generation data is preferable.

(2) If $\bar{Q}_1$ is not known but the mutation rate is known, and if $Q_{1(0)} = U_0/h$, where U_0 is the

mutation rate per chromosome in the original population, the following method is useful. Differentiation of $Q_{1(t)}$ with respect to t gives

$$\begin{aligned}\frac{dQ_1}{dt} &= -(Q_{1(0)} - \tilde{Q}_1)he^{-ht} \\ &= (\tilde{U} - U_0)e^{-ht}\end{aligned}$$

where $\tilde{U}$ is the mutation rate per chromosome in the new equilibrium population. Thus, equating $\frac{dQ_1}{dt}$ to $Q_{1(t+1)} - Q_{1(t)}$,

$$y = -\log_e(Q_{1(t+1)} - Q_{1(t)}) = -\log_e(\tilde{U} - U_0) + ht$$

from which we can estimate h by least-squares methods. The weight for y is given by the reciprocal of the following variance.

$$V_y = \frac{V_D}{(Q_{1(t+1)} - Q_{1(t)})^2}$$

where

$$V_D = \frac{Q_{(t+1)}}{(1 - Q_{(t+1)})n_{(t+1)}} + \frac{Q_{(t)}}{(1 - Q_{(t)})n_{(t)}}$$

In this case $Q_{1(t+1)} - Q_{1(t)}$ should be positive.

(3) If $Q_{1(0)} = 0$ and ht is small, formula (5) is approximately equal to

$$\begin{aligned}Q_{1(t)} &= \tilde{Q}_1(ht - (ht)^2/2) \\ &= \tilde{U}t - \tilde{U}ht^2/2 \\ y &= (\tilde{U}t - Q_{1(t)}) = \tilde{U}ht^2/2\end{aligned}$$

Therefore, if $\tilde{U}$ is known,

$$\hat{h} = \frac{2}{\tilde{U}} \frac{\sum wyt^2}{\sum wt^4}$$

where w is the reciprocal of $V_y = \frac{Q_{(t)}}{(1 - Q_{(t)})n_{(t)}}$

LITERATURE CITED

- CROW, J. F. and M. KIMURA, 1956 Some genetic problems in natural populations. Proc. 3rd Berkeley Symp. on Math. Stat. and Probab. **4**: 1-22.
- CROW, J. F. and R. G. TEMIN, 1964 Evidence for the partial dominance of recessive lethal genes in natural populations of *Drosophila*. Am. Naturalist **98**: 21-33.
- DYER, K. F., 1956 Fitness and competitive ability in irradiated populations of *Drosophila melanogaster*. Mutation Res. **3**: 327-339.
- GOLDBERG, S., 1950 On a singular diffusion equation. Ph.D. thesis, Cornell University (Cited in CROW and KIMURA, 1956).
- KIMURA, M., 1964 *Diffusion Models in Population Genetics*. Methuen, London.
- MILLER, G. F., 1962 The evaluation of eigenvalues of a differential equation arising in a problem in genetics. Proc. Cambridge Phil. Soc. **58**: 588-593.
- NEI, M., 1968 The frequency distribution of lethal chromosomes in finite populations. Proc. Natl. Acad. Sci. U.S. **60**: 517-524.
- PROUT, T., 1954 Genetic drift in irradiated experimental populations of *Drosophila melanogaster*. Genetics **39**: 529-545.
- ROBERTSON, A., 1962 Selection for heterozygotes in small populations. Genetics **47**: 1291-1300.
- TOBARI, I. and M. MURATA, 1968 Effect of X rays on genetic load in a *Drosophila* population. Proc. 12th Intern. Congr. Genet. **1**: 230.

- WALLACE, B., 1956 Studies on irradiated populations of *Drosophila melanogaster*. J. Genet. **54**: 280-293. —, 1962 Temporal changes in the roles of lethal and semi-lethal chromosomes within populations of *Drosophila melanogaster*. Am. Naturalist **96**: 247-256.
- WALLACE, B. and J. C. KING, 1951 Genetic changes in populations under irradiation. Am. Naturalist **85**: 209-222.
- WRIGHT, S., 1937 The distribution of gene frequencies in populations. Proc. Natl. Acad. Sci. U.S. **23**: 307-320.