A BIOPHYSICAL THEORY FOR RADIATION-INDUCED POLYGENIC MUTATIONS*

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Introduction

There has recently been a considerable body of evidence that characteristics of radiation-induced polygenic mutations are substantially different from those of major gene mutations (Scossiroli, 1953; Clayton and Robertson, 1955; Gregory, 1956; Oka *et al.*, 1958; Burdick and Mukai, 1958; Bateman, 1959a, b; Kao *et al.*, 1960; Yamada, 1961; Mukai, 1961). It is a little premature, but we may summarize from these recent papers that polygenic mutations have three major characteristics:

(1) increase in quantitative variance of the polygenic character with increasing radiation dose at least in the low dose range,

(2) more or less symmetrical distribution of the frequency of the number of mutants with the polygenic quantity X about the mean $\overline{X}$ which gives only a small or no deviation from that of the control, $\overline{X}_0$, and

(3) a high mutation rate per locus per unit dose.

This paper is primarily concerned with the derivation of the equation for the polygenic mutation rate per unit dose per locus by generalizing the method adopted by Bateman (1959a) and Mukai (1961); it also represents a crude model of polygenic mutations accounting for the above-mentioned characteristics. An example is given in order to show how to use the theory for estimating polygenic mutation rate, but a detailed theoretical discussion in connection with applications to experimental data will be presented elsewhere.

Theory

1. Relationship between the Radiation Dose and the Variance

Assume that a haploid organism or an individual of an arbitrary isogenic line has n polygene loci with gene $\mathbf{g}_i$ at the corresponding locus i ($i=1, \ldots, n$); $\mathbf{g}_i$ mutates from the wild type $\mathbf{g}_{i0}$ to an allele $\mathbf{g}_{ir}$ with probability p_{ir} ($r=1, \ldots, \nu_i$) where ν_i is the number of all the polygene alleles at locus i: there is one-to-one correspondence between gene $\mathbf{g}_i$ and an enzyme; and the polygenic quantitative character X in arbitrary units is, excluding the environmental variation, a function of $g_1, \ldots, g_n$ which now denote the measures of the activities of the corresponding enzymes. The term "enzyme" will be used throughout this paper in a broad sense so as to include also

*Contribution from the National Institute of Genetics, Japan, No. 366.

any other substance whose specificity is determined by genic material. Then, for small values of $\Delta g_i = g_i - g_{i0}$, we have

$$X(g_1, \ldots, g_n) = X_0(g_{10}, \ldots, g_{n0}) + \sum_{i=1}^{n} \frac{\partial X_0}{\partial g_i} \Delta g_i. \tag{1}$$

This means that the additivity law holds for the resultant effects of simultaneous mutations at the loci as long as Δg_i is small. This limitation on Δg_i is our definition of "polygenic mutation" together with the assumption that n is sufficiently large. In this paper we are concerned only with such "minor" mutations.

For treating discrete changes in g_i, we use the following notation:

$$x_{ir} = X(g_{10}, g_{20}, \ldots, g_{ir}, \ldots, g_{n0}) - X_0. \tag{2}$$

Utilizing the above additivity law and (2), we obtain the probability $f(x)$, that the irradiated organism has the value X equal to $X_0 + x$, as the coefficient of z^x in the expansion of the generating function

$$G(z) = \prod_{i=1}^{n} \left\{ 1 + \sum_{r=1}^{\nu_i} p_{ir}(z^{x_{ir}} - 1) \right\} = \sum_{x=-\infty}^{\infty} f(x) z^x. \tag{3}$$

From (3) we can calculate the j-th moment of x as follows:

$$\mu_j' = \sum_x x^j f(x) = \left(z \frac{\partial}{\partial z} \right)^j G(z)_{z=1}. \tag{4}$$

The variance μ_2 is easily calculated from (4);

$$\mu_2 = \sum_{i,r} p_{ir}(x_{ir})^2 - \sum_i \left(\sum_r p_{ir} x_{ir} \right)^2. \tag{5}$$

Assume that the mutation frequency p_{ir} is related to dose D by

$$p_{ir} = (\exp[-\Sigma c_{ir}' D]) \ (c_{ir}' D)^k / k!, \tag{6}$$

i.e., in the low dose-range,

$$p_{ir} = (-c_{ir}' D)^k / k! = (c_{ir} D)^k, \tag{7}$$

where $(c_{ir})^k$ is the mutation rate per allele at the unit dose and k the constant indicating the number of hits necessary for a mutational event. Then, combining (7) for the low dose-range with (5) we obtain

$$\mu_2 = a_2 D^k (1 - \gamma_2 D^k), \tag{8}$$

where

$$a_2 = \sum_{i,r} (c_{ir})^k (x_{ir})^2; \ a_2 \gamma_2 = \sum_i \left(\sum_r (c_{ir})^k x_{ir} \right)^2. \tag{9}$$

If we assume $k = 1$ as is the most frequent case of major gene mutations, then, from (8) we find that μ_2 should also be a linear function of dose in the low dose-range because γ_2 is usually very small. The linear relationship based on a crude model has been already utilized by Yamada (1960), and his recent experiments with bristle-number in *Drosophila* have indicated no contradiction with the linear relationship (Yamada, 1961).

2. Distribution of the Magnitude of Individual Polygenic Mutations

We may rewrite $\partial X_0/\partial g_i$ given in (1) as follows:

$$x_i=\frac{\partial X_0}{\partial g_i}\Delta g_i=\left(\sum_\eta \frac{\partial X_0}{\partial y_\eta}\frac{\partial y_\eta}{\partial g_i}\right)\Delta g_i;\ (i=1,\ .\ .,\ n) \tag{10}$$

where y_η denotes the amount of a specific substance η (e.g., hormone, water content, etc.) which directly affects the quantitative character X, and η stands for the kind of the end product of a complicated system of biochemical reactions controlled by enzymes g_i's. That is, $y_\eta=y_\eta\ (g_1, g_2, \ldots g_n);\ \eta=1, 2, \ldots$. We now assume that the number of kinds of biochemical systems giving rise to such substances as η is very large and that $\frac{\partial X_0}{\partial y_\eta}\frac{\partial y_\eta}{\partial g_i}$ takes a small absolute value having an almost equal chance of a negative or positive sign for varying η because of the extreme complexity and the balanced system of negative feedbacks in the metabolism of the living organism. Then, from (10) we find that $\partial X_0/\partial g_i$ and hence the magnitude x_i of a polygenic mutation should be distributed in a Gaussian-like distribution for varying i, even though the mean value of Δg_i may deviate from zero toward the deleterious direction as is usually the case for major gene mutations. If this is the case and c_{ir} does not noticeably depend on the locus i, then from (3) the probability distribution function $f(x)$ of the number of mutants with resultant mutation effect x should also take a form similar to a normal distribution function about the mean $\bar{x}$ which is very small or zero as observed by, e.g., Oka *et al.* (1958), Burdick and Mukai (1958), Yamada (1961) and Mukai (1961).

It should, however, be noted that if we irradiate a strain or line whose polygenic character is, before irradiation, appreciably different from the mean of the original wild-type population, we may not be able to assume the above-mentioned balanced mechanism for the strain; hence the mean of polygenic characters of the irradiated group will appreciably deviate from the character of the control towards the mean of the wild types. Furthermore, in some cases the experimental data may not clearly show the change in variances because of the difference in the environmental variances between the control and the irradiated group.

3. High Frequency of Polygenic Mutations

Let ρ denote the ratio of the average frequency per locus per unit dose of polygenic mutations to that of major gene mutations. The experimental data indicate that ρ is very large, e.g., about 10^2 (Burdick and Mukai, 1958) and 30 (Mukai, 1961) for viability mutations in *Drosophila* and about 10^2 for mutations affecting bristle-number in *Drosophila* (Yamada, 1961).

Those results may be most simply accounted for by the following assumptions. The polygenic mutations are types of mutations due to changes in base sequences of DNA molecules which result in the changes of some of the non-essential amino-acid residues of the corresponding enzymes, giving rise to only minor effects on the activities of the enzymes; the major gene mutations are due to changes in DNA-base sequences which

lead to the changes of some of the essential amino-acid residues of the enzymes, giving rise to drastic activity changes or alteration of the control enzymes to other qualitatively different kinds of mutant enzymes; the ratio α of the number of the non-essential amino-acid residues to that of the essential amino-acid residues in an enzyme is on average of the order of ρ; and the radiation effects of DNA-bases are at random.

If the above explanation is valid, then it is a natural consequence that Yamada (1961) has found that the ratio of the polygenic frequency to the major genic frequency for spontaneous mutations is of the same order as that for radiation-induced mutations, and hence the doubling doses for the polygenic and major gene mutations are of the same order, despite the big difference in the absolute values of mutation rates between the polygenic and major gene mutations.

4. Equations for Average Polygenic-Mutation Rate per Locus per Unit Dose

It is almost impossible to carry out the rigorous numerical calculation of the polygenic-mutation frequency per unit dose from (5) combined with (6). We will derive approximate equations for calculating the average polygenic mutation rate per locus per unit dose.

Assume that x_{ir} takes the same value x_i for all the ν_i mutant alleles at locus i, c_{ir} is a common constant c independent of i and r; and ν_i is also a common constant ν. Then, from (5) and (6) we have

$$\mu_2=\nu(cD)^k\exp[-(k!)^{1/k}\nu cD](1-\nu(cD)^k\exp[-(k!)^{1/k}\nu cD])\sum_{i=1}^{n}x_i^2. \tag{11}$$

We can in general define the characteristic dose D_m which maximizes μ_2. For the present case, we have the relation

$$\nu c=\frac{k(k!)^{1/k}}{D_m}. \tag{12}$$

Whether (12) is valid or not is strictly dependent on the validity of (6). The μ_2 has a rather broad maximum.

The μ_2 values found by Kao *et al.* (1960) have a sharp maximum at 20 kr. for X_3 lines of irradiated rice, but the decrease in the μ_2 with dose greater than 20 kr. is too rapid to be accounted for by (11); that is, as Kao *et al.* (1960) pointed out, the decrease of the μ_2 seems to be due to artificial elimination in the X_2 generation of sterile or extremely dwarf plants which were large in number in plots irradiated with high doses. In fact, the μ_2 value-versus-dose curve for the plant heights of the X_2 lines has no maximum and can be well fitted by (8) with $k=4$. However, if there is any organism which fits our assumptions, the method to use (12) for estimation of mutation rate per locus per unit dose, νc, for the case of $k=1$, has a big advantage over the other method to be mentioned because it requires no knowledge about n and x_i.

For estimating the mutation rate by using experimental data in the low dose-range, it would be better to generalize the method adopted by Bateman (1959a) and Mukai (1961) and to use the simultaneous equations for μ_j $(j=1, 2, 3, \ldots)$. Since we are

concerned only with low doses, neglecting higher order terms of p_{ir}, we can approximate (3) by

$$G(z) = \exp\left[-\sum_{i,r} p_{ir} + \sum_{i,r} p_{ir} z^{x_{ir}}\right] = \sum_{x} f(x) z^{x}. \tag{13}$$

Since the moment generating function $m(t)$ can be obtained by replacing z in $G(z)$ by e^t, we have the following equation for the cumulant generating function

$$K(t) = \ln m(t) = \sum_{i,r}\left[-p_{ir} + \sum_{m=0}^{\infty} p_{ir}(x_{ir})^m \frac{t^m}{m!}\right] = \sum_{m=1}^{\infty} \frac{\kappa_m t^m}{m!}, \tag{14}$$

where κ_m is the m-th cumulant of x. Using the relations $\mu_m = \kappa_m$ for $m=1, 2, 3$ and $\mu_4 = \kappa_4 + 3\mu_2^2$, from (14) we obtain

$$\mu_1 = \sum_{i,r} p_{ir} x_{ir} \doteqdot \nu(cD)^k \sum_{i=1}^{n} x_i = n\nu(cD)^k a, \tag{15}$$

$$\mu_2 = \sum_{i,r} p_{ir}(x_{ir})^2 \doteqdot \nu(cD)^k \sum_{i=1}^{n} x_i^2 = n\nu(cD)^k (a^2 + \mu_{2a}), \tag{16}$$

$$\mu_3 = \sum_{i,r} p_{ir}(x_{ir})^3 \doteqdot \nu(cD)^k \sum_{i=1}^{n} x_i^3 = n\nu(cD)^k (a^3 + 3a\mu_{2a} + \mu_{3a}), \tag{17}$$

$$\begin{aligned}\mu_4 &= \sum_{i,r} p_{ir}(x_{ir})^4 + 3\left(\sum_{i,r} p_{ir}(x_{ir})^2\right)^2 \\ &\doteqdot \nu(cD)^k \left[\sum_{i=1}^{n} x_i^4 + 3\nu(cD)^k \left(\sum_{i=1}^{n} x_i^2\right)^2\right] \\ &= n\nu(cD)^k \left[a^4 + 4a\mu_{3a} + 6a^2\mu_{2a} + \mu_{4a} + 3n\nu(cD)^k (a^2 + \mu_{2a})^2\right],\end{aligned} \tag{18}$$

where the third formula of each equation from (15) to (18) is the approximation based on the same assumptions as used for (11); and a is the mean of x_is and μ_{ja} the j-th moment of x_i about a.

Following the argument given in Section 3, we now restrict ourselves to the case that x_is are classified into two groups made up of contributions from n_1 and n_2 loci with mean a_1 and a_2, respectively, and x_is of each group are distributed about each mean in a normal distribution with respective standard deviations σ_{1a} and σ_{2a}. Then, from equations (15) to (18) we obtain

$$\mu_1 = \nu(cD)^k (n_1 a_1 + n_2 a_2), \tag{19}$$

$$\mu_2 = \nu(cD)^k [n_1(a_1^2 + \sigma_{1a}^2) + n_2(a_2^2 + \sigma_{2a}^2)], \tag{20}$$

$$\mu_3 = \nu(cD)^k [n_1(3a_1\sigma_{1a}^2 + a_1^3) + n_2(3a_2\sigma_{2a}^2 + a_2^3)], \tag{21}$$

$$\begin{aligned}\mu_4 = \nu(cD)^k \Big[&n_1(6a_1^2\sigma_{1a}^2 + 3\sigma_{1a}^4 + a_1^4) + \frac{3\mu_1^2}{\nu(cD)^k} + \\ &n_2(6a_2^2\sigma_{2a}^2 + 3\sigma_{2a}^4 + a_2^4) + \frac{3\mu_2^2}{\nu(cD)^k}\Big].\end{aligned} \tag{22}$$

Similarly, we can establish equations for higher order moments. By these seven equations the seven unknown quantities involved can, in principle, be determined, though this method is not very practicable. Bateman (1959a), assuming $\sigma = 0$, considered only one group of x_i, and used μ_1 and μ_2; and Mukai (1961), considering two groups with the assumptions $a_1 = -a_2$ and $\sigma_{1a} = \sigma_{2a} = 0$, used μ_1 to μ_3. Mukai's

estimates $a=0{\cdot}16$ and $vc=1{\cdot}26\times10^{-6}$/r for $n_1+n_2=3000$ and $k=1$ are, respectively, an overestimate and an underestimate because of the neglect of σ_{1a} and σ_{2a}. Since we have neglected the variation of x_{ir} within locus i, the righthand sides of μ_2 to μ_4 in the above equations are underestimates of the actual values.

In conclusion, it should be noticed from (15) to (17) that all the μ_1, μ_2 and μ_3 increase, at least within a low dose-range, at an equal rate (linearly for the case of $k=1$) with increasing dose D.

5. Application of the Theory to Experiments

An example is given in this section in order to show how to apply the theory to experimental data.

If the hypothesis assumed in Section *2* for explaining the symmetrical occurrence of polygenic mutations is valid, then it seems that there is often only one group of x_is. That is, from (19) to (22) we have the following equations for the case of $k=1$:

$$\mu_1 = nvcDa, \tag{23}$$

$$\mu_2 = nvcD(a^2+\sigma_a^2), \tag{24}$$

$$\mu_3 = nvcD(3a\sigma_a^2+a^3), \tag{25}$$

$$\mu_4 = nvcD(6a^2\sigma_a^2+3\sigma_a^4+a^4)+3\mu_2^2. \tag{26}$$

By using (23) to (25), the unknown a ($\neq0$), σ_a and nvc can be uniquely determined from experimental values of μ_1, μ_2, μ_3 and D. The validity of the assumptions used can be checked by substituting the obtained values into (26). The explicit formulae for a ($\neq0$), σ_a^2 and vc are given by

$$a = \frac{3\mu_2}{4\mu_1}\left[1+\left\{1-\frac{8}{9}\left(\frac{\mu_3}{\mu_2}\right)\left(\frac{\mu_1}{\mu_2}\right)^2\right\}^{\frac{1}{2}}\right], \tag{27}$$

$$\sigma_a^2=\tfrac{1}{3}\left(\frac{\mu_3}{\mu_1}-a^2\right), \tag{28}$$

$$vc=\mu_1/nDa. \tag{29}$$

As a measure of the ratio of contribution of loci with positive x_i to that of loci with negative x_i, we may use the value defined as the absolute value of the ratio of the mean of positive x_i multiplied by the number n_+ of the loci with positive x_i to the mean of negative x_i multiplied by the number n_- of loci with negative x_i:

$$\beta = \left[\int_0^\infty x\exp\left\{-(x-a)^2/2\sigma_a^2\right\}dx\right] \Big/ \left[\int_{-\infty}^0 -x\exp\left\{-(x-a)^2/2\sigma_a^2\right\}dx\right]$$

$$=\frac{\left[\frac{\sigma_a}{\sqrt{2\pi}}\exp(-a^2/2\sigma_a^2)+aF(a/\sigma_a)\right]}{\left[\frac{\sigma_a}{\sqrt{2\pi}}\exp(-a^2/2\sigma_a^2)-a\left\{1-F(a/\sigma_a)\right\}\right]}, \tag{30}$$

where $F(y)$ denotes the area under the normal curve (with $\sigma_a=1$ and $a=0$) from $-\infty$ to y. For Mukai's assumption mentioned above β is equal to n_+/n_-.

Results of application of (27) to (30) to Mukai's experimental data are summarized in Table 1. It is interesting to note that as expected the estimate of mutation rate νc is larger than Mukai's (by a factor of 3) while the mean magnitude of polygenic mutation a has turned out to be a reasonably small value which is only $\frac{1}{7}$ of Mukai's estimate.

Table 1. *Analysis of experimental data by equations from (27) to (30) in text*

Experimental data (Mukai 1961)		Values estimated	
		present theory	Mukai (1961)
$\mu_1 = 0{\cdot}02500$	a	0·023	0·16
$\mu_2 = 0{\cdot}009973$	νc†	$3{\cdot}7\times10^{-6}$	$1{\cdot}3\times10^{-6}$
$\mu_3 = 0{\cdot}000660$	σ_a	0·093	..
$D = 100$ r	β	1·9	2·45
$n = 3000$*			

* This is Mukai's assumption.
† The average mutation rate per locus per roentgen.

Discussion

Our definition of polygenic mutation is operational in the sense that the proposed model of polygenic mutations accounts for their major experimental characteristics. The definition is essentially similar to that given by Bateman (1959a). It does not matter whether the polygenes are alleles of major genes or located at different loci. If the latter is the case, then the polygenes will correspond to non-essential enzymes.

Now it should be noted that the equations from (15) to (18) for polygenic mutation frequencies derived from equation (3) apply for any kind of polygenic mutations within a low dose-range provided that the additivity law holds for the resultant effects of simultaneous polygenic mutations (cf. equation (1)). That is, even if the present model turns out to be wrong, the method for calculating the polygenic mutation rate is applicable, even in a case in which a major gene mutation concerning a qualitative character also affects polygenic mutations in another quantitative character which do not give rise to a normal distribution of mutant characters around the character of the control. For example, equations from (23) to (26) are valid if we modify the terms including the standard deviation by introducing appropriate quantities.

The phenotypic response of a higher form to a small change in activity of an enzyme in its cells will depend on the genome condition. For example, let us consider the special case that the second term of equation (1) vanishes because of a certain genome condition such as heterosis in a diploid organism. Then, we have to consider the

second order derivative $(\partial^2 X_0/\partial g_{i0}\,\partial g_{j0})\,\Delta g_i\,\Delta g_j$. This means two and four hits per mutational change in X for $k=1$ and 2, respectively. This four-hit event might be the case for the irradiated rice mentioned in Section 4 and, if so, the Δg_i is due to a two-hit event such as chromosome aberration. However, more careful genetic consideration and experiments should be done before drawing any definite conclusion about these points. If we use, instead of the one-gene to one-enzyme hypothesis, the one-cistron to one-enzyme-polypeptide-molecule hypothesis, then, using the triplet theory, we find an enzyme would be, on the average, made up of several hundred amino-acid residues, among which we may assume the existence of a few essential amino-acid residues. The ratio of the number of non-essential amino-acid residues to that of the essential ones turns out to be about 10^2, which is the same order as the ratio of the polygenic-mutation rate to the major-genic one as inferred in Section 3.

Such a speculation will, however, be too naive. There are many other factors or possibilities to be considered. Enzymes may be classified into non-essential and essential, corresponding, respectively, to polygenes and major genes. Furthermore, genetic material seems to serve also as a regulator of the quantitative aspects of enzyme formation (e.g., Bonner, 1959). The gene itself may have such characteristic response to radiation that a minor change in its function takes place much easier than a major change. Or polygenes may be on different loci and larger in number or more sensitive to radiations than the major genes. The model proposed in this paper is only one of the possible explanations. The hope is entertained that such a biophysical consideration will stimulate interest in polygenic mutation.

It would be interesting to compare the method of calculating polygenic mutation rates as given in this paper with the conventional method for major gene mutations. In the case of major genes, mutational effects are easily distinguishable from environmental variation and the number of mutants is known. That is, the mutational frequency f is a directly measurable quantity as given by the number of mutants divided by that of viable individuals. In mathematical language, the left hand side of equation (15), μ_1, can be separated into f (frequency) times a (magnitude of mutational effect). Therefore, eliminating the common factor a from both sides of equation (15), we have $f=n\nu(cD)$ for the case of major gene mutations with one hit response. Using this equation, from experimental values of f and D we calculate the major gene mutation rate per locus per unit dose, νc, by assuming a proper value for n (number of loci). In fact, the equation (15) includes the case of major gene mutations. On the other hand, the effect of polygenic mutation in each individual is too small to distinguish from the environmental variation, and hence we have to use the equations for higher order moments to estimate the mean value of these effects, a. This means that the polygenic mutation rate calculated as in this paper is on the same basis as the major gene mutation rate calculated by the conventional method provided that the experimental data are good enough to give a reliable value for a. Thus the essential difference of mutation rate per locus per unit dose, νc, between polygenic and major genic mutations, if it exists, lies in the difference of ν (average number of alleles) (Burdick and Mukai, 1958) and/or in c (mutation rate per allele) as discussed above.

SUMMARY

General equations have been derived for estimating polygenic mutation rate per locus per unit dose. It is argued that the present method for estimating polygenic mutation rate is on the same basis as the conventional method for obtaining major gene mutation rate. An example has been given in order to show how to use the equations for calculating polygenic mutation rate.

A crude model has been proposed to account for the characteristics of radiation-induced polygenic mutations: (1) increase in quantitative variance of the polygenic character with increasing radiation dose, (2) more or less symmetrical distribution of the frequency of mutants with changed polygenic quantity about the mean, and (3) a high mutation rate per locus per unit dose.

ACKNOWLEDGMENTS

The author wishes to express his indebtedness to Drs. Y. Yamada and C. Oshima for introducing him to the subject. He is very much indebted to Drs. T. Mukai, Y. Yamada and Y. Hiraizumi for valuable criticism during the development of the theory. Thanks are due to Dr. C. Auerbach for correcting the English, and to Misses H. Isiwa and K. Ishii for preparing the manuscript. The work has been supported by grants from the Ministry of Education of the Japanese Government and the International Atomic Energy Agency.

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