ON THE INTERPRETATION OF THE DOSE-FREQUENCY CURVE IN RADIOGENETICS

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IN a recent paper with the above title by OPATOWSKI (1950) and in another by OPATOWSKI and CHRISTIANSEN (1950) it is asserted that the observed linear relationship between the number of lethal gene mutations induced in Drosophila and the X-ray dose producing them is compatible with a "multi-hit" theory of genetic damage. OPATOWSKI sets up a simple "multi-hit" theory and deduces from it certain formulae which agree excellently with the experimental results. His conclusions are vitiated, however, by an error in the mathematical argument and, when this is corrected, the experiments of SPENCER and STERN (1948) are seen to be incompatible with the multi-hit theory he sets up.

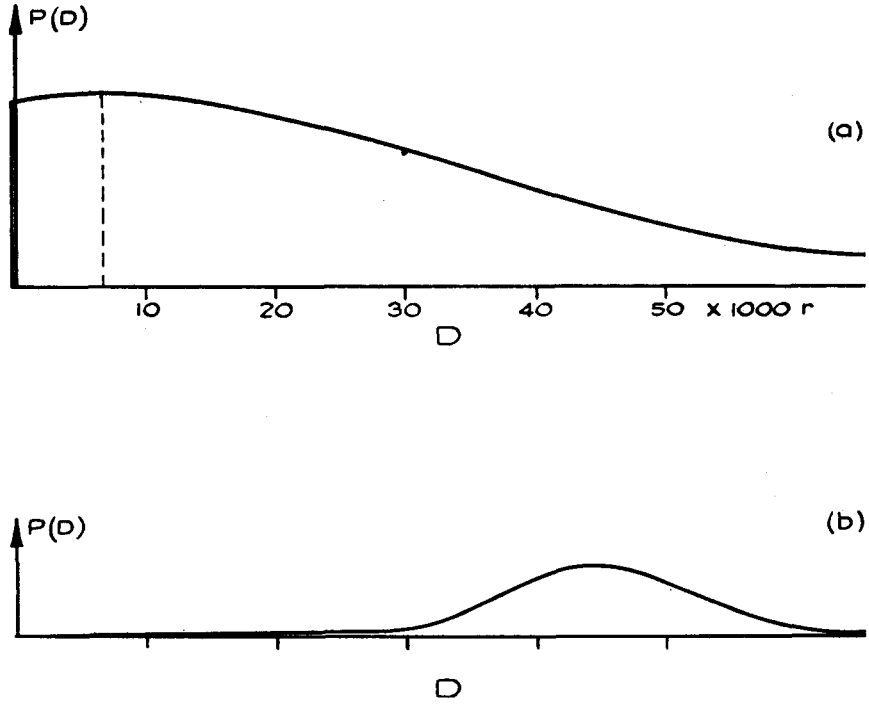

FIGURE 1.—A comparison of the distribution of D derived by OPATOWSKI (a), with the type of distribution predicted by statistical theory (b).

OPATOWSKI postulates that n events (ionizations) must occur within the gene (or in its near neighbourhood) in order to produce a mutation of the type considered, the i^{th} event requiring an increment in dose ΔD_i over the dose at which the $(i-1)^{th}$ event occurred. If the primary ionisations are distributed in random fashion throughout the irradiated volume the individual increments in dose ΔD_i can be taken to be positive random variables. The dose required to produce a mutation is then $D = \sum_{i=1}^{n} \Delta D_i$ and, if n is large, this sum, D, should tend to be normally distributed, irrespective of the parent frequency distribution of the ΔD_i. This is a well-known result in statistical theory (the Central Limit Theorem) but it is important to examine clearly its application to the present problem. OPATOWSKI fails to do this and arrives at a distribution which is contrary to the theorem. His method of selecting a suitable "normal" distribution is to take a normal curve truncated at an arbitrary point, $x = -S$, and choose the two parameters, h and M, of the normal curve and the extra parameter, S, thus introduced, in such a way as to fit SPENCER and STERN's data. The values chosen are S = 42 roentgens, M = 6600 roent-

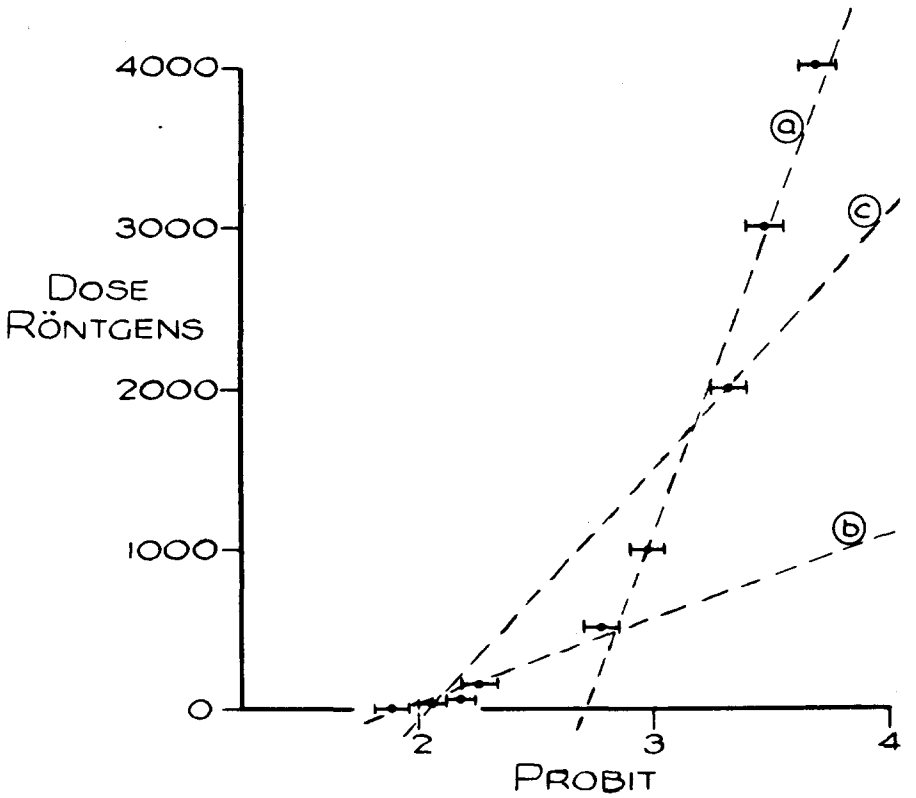

FIGURE 2.—Probit diagram for the data of SPENCER and STERN. Lines (a), (b) and (c) represent normal curves, but none can be found which fits all the data.

gens, $h = 2.5 \times 10^{-5}$ (roentgen)$^{-1}$. The shape of the distribution having these constants is shown in figure 1 a. It bears no resemblance to the distribution of the sum of n positive random variables drawn from any continuous frequency distribution. This sum should tend toward the normal form and should therefore look like figure 1 b for large values of n, where the ordinate at D = 0 of the best fitting normal curve is very small indeed.

The most convenient way of testing whether SPENCER and STERN's data can be fitted by a normal curve is the method of probits (FINNEY 1947). In figure 2, this test is applied to their data and it can be seen that the departure from linearity in the probit diagram is clearly significant. No normal curve can be found, therefore, which fits the data over the whole range. The limits of error shown in this figure are the fiducial limits for a fiducial probability P = 0.95, and are those quoted by SPENCER and STERN (1950, table 3).

The semilogarithmic coordinate system chosen by SPENCER and STERN and also by OPATOWSKI to represent the results does not demonstrate very clearly the high accuracy of the experimental data for low doses. It is better to use double logarithmic scale, as in figure 3. Moreover, since it appears that the induced mutation rate is linear with respect to dose, the spontaneous rate

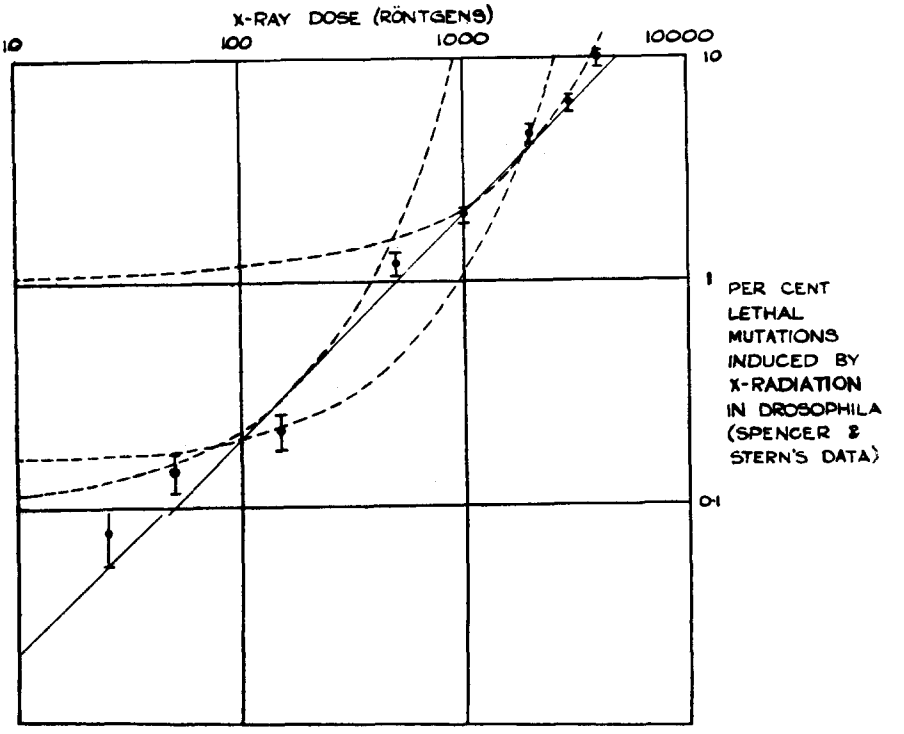

FIGURE 3.—Double logarithmic plot of SPENCER and STERN's data. The three dotted curves correspond to the normal distributions (a), (b) and (c) of Figure 2.

should simply be subtracted from each of the observed total mutation rates to obtain the induced rate, the standard error being increased accordingly. SPENCER and STERN's data have been plotted in this way in figure 3 and they do not appear to depart in any systematic way from a straight line, although a χ^2 test gives $P = 0.015$, which is not very convincing proof of linearity. The main contribution to the high value of χ^2 comes from the points at 150 and 4000 roentgens. Cumulative normal curves corresponding to the lines a, b and c in figure 2 are also drawn and it is quite clear that no normal curve fits the data over the whole range.

Summing up, we conclude, contrary to OPATOWSKI's view, that the experiments of SPENCER and STERN are not consistent with a multi-hit theory of genetic damage.

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