Gamma Rays and the Concept of a Threshold Dose

The report by Furcinitti and Todd (*1*) leads me to a philosophical observation. Workers in this field of research are accustomed to using linear dose coordinates because they expect to find linear or quadratic cause-and-effect correlations. Since the data reported (*1*) extend from 1300 rads down to 21 rads, it was a simple matter for the authors to justify extrapolating the short rest of the way down to zero. The question is, is this valid?

By way of contrast, neutron physicists are accustomed to considering logarithmic energy scales because significant new effects occur over each new energy decade. Although the analogy is admittedly farfetched, note that for radiation dose values, 200 rads is in the vicinity of direct cause and effect for humans, while 20 rads is in the area of statistical cause and effect; the value of 2 rads represents the range of experience with radiation effects in utero, while 0.2 rad is in the vicinity of annual natural background radiation. Surely this suggests that each separate decade has individual significance and deserves some effort to be represented by its own data.

The concept of a threshold is independent of the linearity of the cause-effect curve. The straight line does not need to go directly through the origin, as assumed in the authors' fits, but rather it may intercept at a small positive value. An intercept at 100 percent survival between 0.2 and 2 rads would not at all be inconsistent with the data and error bars presented in figure 2 of (*1*) (see Fig. 1 herein). Confirmation that the given 21-rad data point is truly anomalously high can only be obtained by adding data points at lower doses.

Furcinitti and Todd present a strong experimental case at what I consider to be high dose levels. However, the low dose values are the important ones for radiation protection purposes. In this range, direct and indirect radiation effects may compete with one another and be seriously affected by the statistics of the process. In this case we have no a priori right to conclude that recovery is the only mitigating circumstance.

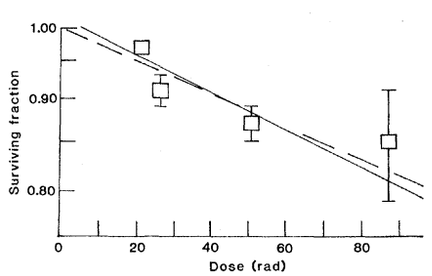

Fig. 1. An alternative fit (solid line) to Furcinitti and Todd's data [figure 2 in (1)], with a nonzero intercept.

I commend the authors on the quality of what appears to be a painstaking experiment, and encourage them to extend their data to lower dose values.

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Reference

1. P. S. Furcinitti and P. Todd, *Science* **206**, 475 (1979).

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Nothing in the data or analysis presented by Furcinitti and Todd (*1*) supports the title or the last sentence of the abstract: "There appears to be no threshold for the lethality of radiation to human cells in vitro."

To determine which of two competing theories is correct, it is not sufficient to show that one of the two theories gives a good fit to the data. It is necessary to show that one of the theories gives a significantly better fit to the data than the other.

There is an obvious fallacy in evaluating a constant by fitting dose data, and then drawing inferences from the fact that the constant has the same value at zero dose as it has at finite dose. Neither of the two exponential forms [see equation 1 or 2 in (*1*)] allows for the existence of a threshold dose, and thus no inferences can be drawn about a threshold dose unless the fit to one of these equations is perfect, which it clearly is not.

The linear fit discussed in the legend of figure 2 in (*1*) does allow for the existence of a threshold, although the authors apparently did not recognize this. A linear relation between dose above a threshold and the surviving fraction of cells is described by the equation

$$S = 1 - C(D - D_0) \quad (1)$$

where S is the surviving fraction of cells, D is the dose in rads, D_0 is the threshold dose, and C is the slope with units of rad^{-1}. This equation can be rewritten as

$$S = I - CD \quad (2)$$

where the intercept I equals $1 + CD_0$.

Clearly, additional measurements with improved accuracy will be necessary to resolve the threshold question. Further efforts should be concentrated on multiple dose measurements, with its effective multiplication of the threshold. In addition, total dose should be limited to the lowest dose consistent with accuracy so as to maximize the effect of threshold on survival fraction.

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Reference

1. P. S. Furcinitti and P. Todd, *Science* **206**, 475 (1979).

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Many comments on our report (*1*) were received. Those of Rydin and LePage embody the substantial statements of most of them. In the context of modern radiation biology we were testing the "linear hypothesis" for cell survival against other models of radiation action, such as the "threshold hypothesis," that predict that the dose-response curve has a zero slope at the origin (zero dose). It is regrettable that misleading statements concerning the relevance of our findings to radiation carcinogenesis have been made in a review of our report (*2*). Our findings concerning cell death are not a cause for revision of any currently accepted radiation exposure and protection standards since these are determined on the basis of genetic and carcinogenic effects and not on the basis of cell death. We calculated that the radiation dosage to which the average American is annually exposed (about 170 mrad) kills about 40 cells per 100,000 exposed. That is fewer by far than the number we lose through natural causes, such as taking a shower, aging, wounds, infections, and digestion. We also conducted our study with radiation therapy in mind, since it is a significant conclusion that 1 rad will kill millions of cells in a volume of tissue weighing 10 g. It remains to be determined whether, as in the case of cell death, the expression of mutations and malignancy follow a "linear" or "threshold" relationship with respect to the effects of radiation on genes or some other cellular target.

We attempted to maximize the statistical accuracy of survival measurements (a small difference between two large numbers) using the optimum research resources at our disposal. At the lowest possible doses where cell killing could be significantly detected, the dose-response curve on a semilogarithmic plot was a straight line with a slope very different from zero at zero dose. Outside this context of model testing, however, Rydin, LePage, and others have suggested (quite reasonably) that this straight line,

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which is consistent with the "linear hypothesis," does not go through the origin (zero cell killing at zero dose). If the data we presented are carefully examined, it is true that there might also be zero cell killing at about 6.0 ± 7.7 rads when the best-fitting straight line is extrapolated to zero cell killing. This extrapolation was also pointed out in the legend to our figure 2 (*1*), which stated that a best-fit straight line not constrained to go through the origin intercepted the ordinate at 1.018 ± 0.022 at zero dose, not 1.000 as the no-threshold hypothesis would imply. The explanation for this extrapolation is a simple one, and we should probably apologize for only referring to it (*3*) and not mentioning it explicitly in our report. At the time of irradiation up to 4 percent of the colony-forming units in the cultures contained two cells instead of just one so that the measured survival is that of the two populations. Since 96 percent of the cells were single and 4 percent of the colonies had two cells at the time of irradiation the survival S at low doses is given by

$$S = 0.96\, e^{-CD} + 0.04[1 - (1 - e^{-CD})^2] \quad (1)$$

where D is dose, and the coefficient C has the value we reported. Equation 1 is conceptually more consistent with the experimental design than the relationship

$$S = S_0 e^{-CD} \quad (2)$$

which also extrapolates to $S = 1.018 \pm 0.022$ at zero dose, or the relation

$$S = I - CD \quad (3)$$

suggested by LePage.

The value of reduced χ^2 for the fitting of Eq. 1 was found to be 2.3, but when we attempted to fit threshold-dependent functions suggested by Rydin, LePage, and other respondents, we found χ^2 values between 3.0 and 4.0. We did not consider the possibility of ignoring any of the data points as some other respondents wished to do.

Concerning the meaning of "high" and "low" doses, in the context of sensitive biological end points such as malignant transformation (*4*), a dose of 20 rad is high. Cell transformation can be detected around 1 rad because it is measured above a small zero-dose background incidence. Somatic cell survival, whether in vitro or in vivo, must be measured as a difference between two large numbers. For example, to measure cell survival after 5 rads, which we predict to be 98.5 percent, would require the counting of at least 10^5 colonies, irradiated and control, to obtain statistical significance. Beyond a priori statistics, superimposed technical error limits make such a measurement nearly impossible. Since our result, which improved substantially on the statistics presented in early work (*5*), did not change the original conclusion that cell killing is a linear function of dose at low dose, we did not commit research resources to further refinements.

We are delighted that Rydin and LePage and others have been stimulated by our study to give critical thought to the issue of biological dose-response relationships for ionizing radiation effects.

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4. C. Borek and E. J. Hall, *Nature (London)* **243**, 450 (1973).
5. G. W. Barendsen, *ibid.* **143**, 1153 (1962).

23 June 1980

High-Grade Fuels and Biomass Farming

Weisz and Marshall (*1*) have presented a distorted view of both the energetics and economics of ethanol production via biomass fermentation. Their conclusion, that with current technology ethanol production represents a net consumption of fuel, results from use of an unrealistically high processing energy and neglect of energy credit for the distillers' dry grains. There are firms currently designing and constructing fermentation ethanol plants (*2*) with processing energy requirements in the range of 1.71 to 0.46 GAL (energy-equivalent gallons of fuel) (*3*) as compared to the value of 3.92 GAL used by Weisz and Marshall (part B in their figure 4). Although they allowed a credit for distillers' dry grains in their economic analysis, they ignored this in their energy analysis. Inclusion of this credit would reduce the cultural energy input, A, by one-third, resulting in $A = 0.75$ in their figure 4. Fuel efficiency must, indeed, be incorporated into the energy analysis, but for gasohol, the alcohol-containing motor fuel most likely to be implemented, the literature contains conflicting accounts (*4*). Weisz and Marshall in considering the best possible case, equal fuel efficiencies (miles per gallon) for ethanol and gasoline, arrive at the conclusion that "the system would remain a net fuel consumer." However, with the more realistic figures cited above the best possible case for current technology results in a net fuel production ranging from 0.14 to 1.39 GAL.

Under the subheading *Proposed improvements* their "most optimistic case" is subject to the same flawed analysis. Using the energy credit for distillers' dried grains and fuel equivalency (equal miles per gallon) for ethanol and gasoline one obtains 4.68 GAL resulting from an input of 1.33 GAL, a net production of 3.35 GAL as opposed to their result of 1.1 GAL. Even when fuel efficiency is based on volumetric energy content (*5*) the results are 3.1 GAL resulting from an input of 1.33 GAL for a net production of 1.77 GAL.

Even more serious was their failure to use insights available through the second law of thermodynamics. They ignored the quality of energy and presented their results simply in terms of GAL's (Btu's). Conspicuously absent is the realization that the ethanol-via-biomass process requires mainly low-level heat for such tasks as cooking, by-product drying, and distillation. Today, many well-managed petroleum refineries and chemical-manufacturing complexes have an abundance of low-pressure steam that could be used for ethanol production. Also, cogeneration of electricity and low-pressure steam would be effectively incorporated into future ethanol production facilities. Whether these sources of low-quality energy will be utilized, of course, depends on the existence of the necessary economic incentives; however, a proper energy analysis should recognize this potential advantage.

A strange brand of economics, based on net fuel production, was used to arrive at an excessively high cost for ethanol which was referred to as "consumer outlay." This economic artifact was then compared with the market price of methanol and coal-derived fuels leaving the reader only to conclude that ethanol manufacture is prohibitively expensive. All processes are subject to efficiencies (first or second law based) less than unity; however, because of "free," and thus uncounted, solar energy the agricultural operation that produces biomass returns us more energy than expended. Thus, a total process that includes a bio-

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