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The Biophysical Stage of Radiation Carcinogenesis*

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Abstract

The dependence of the induction of cancer on the absorbed dose of ionizing radiations has been specified in terms of increasing complexity. The first notion of simple proportionality (the "linear hypothesis") is now frequently replaced with a dependence on both the first and second powers of the dose (the "linear-quadratic model") which implies proportionality at low doses only. Microdosimetric considerations and in particular the theory of dual radiation action would be in accord with this relation if tumors were to arise from single cells as the result of a transformation that is autonomous (i.e., depends only on the radiation received by the cell). In this case it must be expected that the linear portion of the dose-effect curve is dose rate independent but that the quadratic component may decrease with decreasing dose rate because of repair during the interval between two events (energy depositions by individual particles). Various data appeared to be in agreement with this picture.

However it was shown some time ago that the dose-incidence relation of a neoplasm indicates a non-autonomous response because of departure from a linear dependence when the mean number of events in cells is much less than one in neutron irradiations.

Another discrepancy is the repeated observation that reduction of dose rate, while resulting in the expected lessening of the effectiveness of low-LET radiation, increases the effectiveness of neutrons (especially in the case of oncogenic cell transformation). As will be shown, it is possible to

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account for this phenomenon although at this point the limitations of the available data make the explanation semi-quantitative and therefore still somewhat hypothetical. However, it should be noted that it does not even require a non-autonomous response and thus is at least an example of the complexities that can arise in the earliest (biophysical) stage of radiation carcinogenesis.

Keywords: radiation carcinogenesis, cell transformation, microdosimetry, radiation protection, dose-effect relations, dose-rate effects

Introduction

The quantitative relation between absorbed dose and radiation carcinogenesis has two major aspects that may be termed scientific and practical. The former concerns the acquisition of more precise knowledge and possibly conclusions on mechanisms; the latter is involved in the provision of numerical data for radiation protection.

The nature of the dose-effect relation for carcinogenesis has become of major concern in radiation protection in recent years because of a trend in which limitation has been replaced by assessment (Rossi 1985). Rather than merely recommending maximum values of permissible dose equivalents, the magnitude of the risks attendant to any dose equivalent is postulated. This permits expansion of the scope of radiation protection and the formulation of such quantities as the dose equivalent commitment and the effective dose equivalent (ICRP 1977; ICRP 1978; ICRP 1980). The validity of this approach evidently depends on the nature of the dose-effect relation and in practice on the assumption that risk is proportional to dose and independent of dose rate (the "linear hypothesis").

Earlier analyses, such as the BEIR I Report (NRC 1972), tended to support this position, but various experimental findings and theoretical considerations indicate that it can not apply beyond doses of low-LET radiation that are of the order of one gray because at these, and corresponding lower doses of high-LET radiation, the RBE is generally observed to depend on the level of effect (or equivalently on the absorbed dose of either radiation) so that, at least for one of the radiations, a non-linear dose-effect relationship would apply. Although evidence from radiation epidemiology is suggestive, this dependence has not been established for human radiation carcinogenesis. Nevertheless, in view of

its proven existence in the great majority of experiments involving other higher organisms, it seems unlikely that it does not apply to man. Another very common finding in experimental radiobiology is that, at least in the case of low-LET radiation, effectiveness depends on dose rate at sufficiently high doses.

These as well as other findings have motivated doubts as to the validity of the linear hypothesis. In BEIR III (NRC 1980), the preferred analytic approximation to dose effect relations in carcinogenesis is the so-called "linear-quadratic model" for low-LET radiation. In this modification the linear dependence is augmented by a quadratic one and the probability, p, of cancer induction by an absorbed dose D (sufficiently small to allow for full cellular survival) is given by

$$p = \alpha D + \beta D^2 \qquad (1)$$

where α and β are constants. β is assumed to depend on the dose rate and the quadratic term is taken to be of negligible importance in radiation protection because doses comparable to α / β are assumed to be accumulated only over long periods of time. In line with this view it has been stated that unless a dose-rate effectiveness factor (DREF) is applied, linear interpolation of human cancer incidence data between high and zero dose, overestimates the risk at low doses of low-LET radiation (NCRP 1980). For high-LET radiation α/β was considered so large that any error involved is small.

These general considerations have formed the basic justification for adherence to recommendations on radiation protection that are based on a proportionate dose-rate-independent relation between probability of carcinogenesis and absorbed dose.

Experimental Evidence

Attempts to verify Eq.1 on the basis of observations are subject to well-known limitations. One of these concerns the statistical precision attainable with a sample of practical size. The other is the difficulty in identifying suitable controls in epidemiological studies. A third aspect which interacts with both of the preceding ones is the degree of "spontaneous" carcinogenesis (the control incidence).

There is no a priori reason why there should be an invariant shape of the dose-effect curves for carcinogenesis, and data obtained in experimental radiobiology certainly disclose a great variety of curves (Rossi 1985). However, these obtain at doses that are of little concern to radiation protection. Although long-term occupational exposure near maximum permissible levels could result in a total of several sievert of whole body or organ dose equivalent, such values are not only unusual, but comparison with radiobiological data would presuppose dose-rate independence over many years in which the more radiosensitive cells may have divided repeatedly. By and large, the principal interest of radiation protection concerns the effect of dose equivalents that are of the order of 10 mSv. Indeed, in many considerations of population exposure, levels that are well below the annual dose equivalent from background radiation ($\sim$1 mSv) are considered. The question whether proportionality generally obtains for dose equivalents of this order is very unlikely to be answered in experimental radiobiology. The magnitude of the interpolation required may not be obvious in the usual linear (rather than logarithmic) form of presentation in which the doses of concern in radiation protection extend over a minor fraction of the straight line drawn between the incidences at zero dose and at the lowest dose point.

In general, epidemiological surveys suffer even more from these

deficiencies. Figure 1a shows the incidence of breast cancer in the A-bomb survivors in Nagasaki. The fact that the estimated breast dose is based on the probably somewhat incorrect TD65 estimate is inconsequential in view of the large statistical uncertainties in even this sample which is by far the largest for which we currently have reasonably accurate dose information. The assertion that this is a case of "linear dependence" (NRC 1980) is difficult to accept and the degree of possible error in assessing risks in routine radiation protection becomes obvious when the data are plotted logarithmically (Fig. 1b). The fact that the data can not be said to be inconsistent with proportionality does not eliminate the large variations in the low dose risk if dependences are considered which are only slightly different at higher doses.

Studies attempting to correlate cancer mortality to local background in extensive geographical areas deal with such large populations that the mortality in each region is known with great precision. The studies have nevertheless resulted in contradictory conclusions with both positive and negative correlations being found. The reason is doubtlessly the variability of cancer induction by other environmental agents and demographic factors. At this point and in the foreseeable future, epidemiological evidence alone can not establish whether doses of a few milligray are detrimental, ineffective, or even beneficial.

General Considerations on Cellular Effects

Eq.1 has the same form as the principal tenet of dual radiation action (Kellerer and Rossi 1978). Although this theoretical approach is concerned with the yield of lesions, this may be considered to be an adequate representation of the probability of cellular effects if these are

produced by independently-acting lesions.

On the basis of more general and simpler microdosimetric considerations, the validity of the linear term in Eq.1 may be expected for absorbed doses that are so small that the average number of energy depositions by charged particles (in the following termed events) is much less than one. Under these conditions the spectrum of energy losses is dose independent and a change of dose merely changes the fraction of cells receiving energy. Since the event probability is proportional to the dose, the effect probability must likewise be. It can be shown that even when the mean event frequency is small, there can in fact be a dose-rate effect under certain conditions (Rossi and Kellerer 1986). However these seem to be unlikely and barring their occurrence one may assume that proportionality obtains over the entire dose range of major concern in radiation protection. In line with the reasoning given thus far, one might also believe that at larger doses a reduction of dose rate can only lessen effectiveness. However, as discussed below, the opposite can be true.

The question whether tumor development parallels cell injury involves the issue of autonomous response.

The Autonomous Response

In the following, the term alteration will be employed for an initial change that causes, or may contribute to cause, a malignancy. If the probability of malignancy as a function of dose is to have the same shape as that for cellular alteration, it is necessary that a) malignancy be produced independently by altered cells, and b) the product pkN (k=probability of malignancy/altered cell, N=number of cells at risk) be significantly smaller than 1.

The possibility that cancers can not develop unless several contiguous cells are altered has been considered (Failla 1958), but more recent findings (Fialkow 1976; Nowell 1976) would appear to support the monoclonal origin of cancer, i.e., a process in which the tumor arises from a single altered cell after repeated divisions.

It is widely accepted that systemic (e.g., immunological, hormonal, etc.) factors can have a profound inhibiting or promoting influence on cancer development, but if their action is dose independent, such modifications can only change the amplitude and not the shape of a dose-effect curve for cell alteration because they multiply it by a constant factor. Under such conditions the cell may be said to be autonomous, and if cancers are monoclonal, proportionality is likely to exist if the number of events per cell is substantially smaller than 1. On the other hand if the modification is dose dependent, i.e., cancer development is influenced by radiation received outside the altered cell, the microdosimetric argument is invalid.

While lack of autonomy could take a variety of forms, a conceptual example is a limited immunological response which suppresses or eliminates altered cells only if they occur in small numbers. One may speculate that such a reaction may cause the occasionally noted reduction of "natural" cancer incidence by moderate doses of radiation by eliminating altered cells present before irradiation.

Experimental indication of the absence of autonomy is the absence of proportionality when the event frequency per cell is substantially less than one. In the case of low-LET radiation this requires doses that are far too low for measurable cancer incidence. Even in the case of high-LET radiation exceptional sensitivity is necessary. This has been found for induction of

mammary neoplasms of the Sprague-Dawley rat by neutrons and deviation from autonomy was observed (Rossi and Kellerer 1972). In view of the later discussion, it is of interest that the departure from proportionality is negative. The various dose-effect curves obtained in neutron carcinogenesis studies may also suggest but do not clearly prove lack of autonomy (Rossi 1985).

Cell Transformation

It would seem that in view of the apparent complexity of the processes leading to radiation carcinogenesis some aspects of its early cellular phase might be usefully investigated by studies of in vitro cell transformations. This not only eliminates modification by systemic responses but permits an accurate assessment of the number of cells at risk and of the relation between cell transformation and cell killing. It is generally recognized that cells that are transformed at a detectable rate may be unusual and differ from those involved in animal carcinogenesis. Nevertheless their study may disclose common characteristics that are more readily investigated in the in vitro system.

From both radiation protection and mechanistic viewpoints two issues are of immediate importance, namely, the shape of the dose-effect relation, and the effects of dose rate on it. On both issues there appear to be discrepancies in experimental reports. For acute exposures to low-LET radiation the dose-effect curves range from simple shapes [linear dependency (Terzaghi and Little, 1976), or biphasic—two lines of different slopes (Little 1979; Bettega et al. 1985)] to more complex [for instance in Hall and Miller (1981) a curve is reported having an initial linear portion followed by a "plateau" between 0.3 and 1 Gy, followed by a quasi-quadratic

shape which eventually saturates at about 10 Gy]. While most of these curves appear to have a negative curvature (i.e., probability per unit dose decreases with increasing dose), it is not clear whether this is associated with low doses only [as in Little (1979) and Hall and Miller (1981)], or is simply a result of the fact that the probability of transformation (or at least that part depending on radiation) must eventually reach its maximum values (i.e., 1). It appears therefore that factors other than dose, and obviously not controlled in these experiments, affect the resulting curves.

The internal consistency of a set of transformation data can be checked simply by repeating the experiment with doses delivered in two fractions separated such that the two dose fractions act independently of each other. If independence obtains, one would expect

$$p(D_1 + t + D_2) = p(D_1) + p(D_2) - p(D_1)p(D_2) \qquad (2)$$

where $p(D_1 + t + D_2)$ corresponds to the fractionation regime described above and $p(D)$ is the transformation probability after an acute dose D. In particular if $p^2(D) \ll p(D)$, one has:

$$p(D + \Delta D) = p(D) + \frac{dp(D)}{dD}\ \Delta D \qquad (3)$$

$$p(D + t + \Delta D) = p(D) + p(\Delta D) = p(D) + \frac{dp(0)}{dD}\ \Delta D \qquad (4)$$

By comparing Eq.3 (acute exposure to dose $D + \Delta D$) to Eq.4 (fractionated exposure to D and ΔD separated by a large interval, t) it is clear that for curves with negative curvature, i.e., for which

$$p'(D) < p'(0) \qquad (5)$$

fractionation enhances the effect -

$$p(D + t + \Delta D) > p(D + \Delta D)\ ,$$

while the opposite would be true for shapes of positive curvature (Rossi 1981). It is very important to realize that p(D) in the expressions

above refers only to that alteration event (among perhaps many others leading eventually to transformation) which is due to radiation. Assuming that a plateau is reached at high doses, p(D) should be normalized to 1 in this region. It is also clear that similar effects should be expected if instead of splitting the dose, protracted exposures are used.

The experimental evidence is again contradictory. There have been reports of enhancement (Hall and Miller 1981; Little 1979; Miller and Hall 1978; Miller et al. 1979) as well as suppression (Han et al. 1980a; Han et al, 1980b; Han et al. 1983; Hill et al. 1984; Watanabe et al. 1984) in the transformation yield at low doses (<1 Gy) when the dose rate is reduced or the dose is fractionated. Interestingly enough only the data of Hall and Miller (1981) (corresponding to the most "complex" shape mentioned above) has been submitted to the test of Eq.2. The fractionation data (Hall and Miller 1981), showing enhancement at low doses and suppression at high doses, were indeed obtained--via Eq.2--from the single-fraction exposure probabilities.(a)

When the test, Eq.2, fails it might be assumed that confounding factors affect the results. A recent paper (Lurie and Kennedy 1985) gives an interesting such example: it is shown that dose-rate effects are significantly different if cells are allowed to grow during exposure of if they are in plateau phase. Another example, obviously contradicting Eq.2, would be a system displaying a linear function as well as dose-rate effects. Although this appeared to be the case in an important series of experiments (Hill et al. 1984), an alternate interpretation is possible (again in terms of a confounding factor) as shown in the next section.

(a) The expression, Eq.2, relates the shapes of dose-effect curves at different dose rates, or fractionation regimes to the curve for acute exposure without actually specifying the latter.

Dose-Rate Effects in Autonomous Action

It is not known whether the cells transformed in tissue culture are autonomous. The fact that the yield of transformants per survivor can depend on the number of cells in the irradiation dish indicates modification of cellular response by events occurring outside of the cell, but it is not clear whether these are dose dependent. It is in any case a matter of interest whether the dose-rate dependence of oncogenic transformations can be accounted for, assuming that they are autonomous. While the positive correlation of dose rate and effectiveness observed at high doses can obviously be explained in terms of repair processes, there appears to have been no explanation of the negative correlation except for a hypothesis that attributes the effect to variation of sensitivity during the cell cycle (Rossi and Kellerer 1986).

The numerical analysis was based on data obtained with fission neutrons at high and low dose rate (Hill et al. 1984). The results obtained in fractionation experiments are in general agreement with the latter (Hill et al. 1985). Figure 2a shows these data by Hill et al. for acute (.103 or 380 mGy/min) neutron irradiation in a logarithmic plot. The solid lines are those given by the authors. It was however pointed out (Barendsen 1935; Elkind and Hill 1985; Rossi and Kellerer 1986) that in light of the reasoning already presented the two lines must join at sufficiently small doses where the event frequency becomes appreciably less than one. It is possible to consider an abstract mechanism whereby the responses may be different at low event frequencies (Rossi and Kellerer 1986) but this is considered to be radiobiologically unlikely and can in any case only delay the ultimate junction of the two lines. Consequently, at least one of the two relations can not be proportionate and Figure 2 may be considered as an

example of the misleading impression of proportionality when relatively precise data at low doses appear to fall on a straight line that passes through the control frequency at zero dose.

Attached C3H 10T1/2 cells have a rather large geometrical cross section and unit event frequency in the nucleus may occur at absorbed doses (of the neutrons employed in these experiments) around 15 mGy (Rossi and Kellerer 1986) although a higher estimate has been given (Hill et al. 1984). Any value of the appropriate frequency must be uncertain since the gross sensitive volume (gsv) for transformation may be smaller and conceivably even bigger than the nuclear volume, but it certainly is possible that the high-dose-rate data do not include doses low enough to correspond to unit event frequency in the gsv.

The fact that low- and high-LET experiments by others have indicated the existence of a plateau, and the related increased effectiveness at low dose rate, the dashed line in Figure 2 seems a more likely way in which the curves join near the origin rather than a deviation of the low-dose-rate curve. It should be pointed out however that concurrent gamma-ray experiments by the investigators who produced the data in Figure 2 did not indicate a plateau or the corresponding inverse dose-rate effect.

A plateau in the dose-effect curve could be due to the existence of a small highly-sensitive fraction of the cell population, that is altered (but not necessarily focus-forming) by a few tens of milligray, while a bigger more resistant fraction contributes a more slowly-increasing but ultimately much larger number of altered cells. The dependence on dose rate can then be explained by variation of sensitivity with cell age. This becomes evident if one considers a simpler situation in which cells are sensitive to alteration during a fractional period τ of the cell cycle and entirely

resistant during the remaining fraction $1-\tau$. In this case an arbitarily large instantaneous dose can alter only a fraction of the population that is equal to τ while protraction of irradiation over a time t can alter a fraction $\tau+t$ if the dose rate is high enough. This requires that the cells are progressing through the cell cycle normally during the irradiation period. Except for possible retardation at higher doses this condition was presumably met because they were in an incubator at optimum growth conditions.

The detailed analysis of this model is given elsewhere (Rossi and Kellerer 1986). Here only the two major consequences should be mentioned. They are that a single neutron secondary (primarily a proton) has a high probability of causing the alteration during the sensitive phase and that the sensitive period lasts for only about 10 minutes during the 24-hour cell cycle.

The calculated response for high dose rate and low doses is given by the dashed line. It is of interest that the overall pattern resulting from these changes is similar to that reported by others for low-LET radiation except for a shift to lower doses because of the high RBE of neutrons.

If the reason for this pattern is the existence of high sensitivity during a brief period in the cell cycle, differences in environmental conditions that change its duration can be expected to result in substantial alterations of the pattern. This could be a reason for varying results obtained by different investigators.

Figure 2b depicts the information in Figure 2a in a linear plot. Except for the difference at high doses in protracted irradiation, the solid and dashed curves in Figures 2a and 2b fit the data equally well.

Regardless of the interpretation given, these figures indicate that for

transformation of C3H 10T1/2 cells, common notions on the high dose-rate dose-effect relation for neutrons are not supported by experimental evidence because:

1. Proportionality obtains only at very low doses ($< \sim 10$ mGy) if the dose rate is high,
2. The early part of the relation has negative curvature,
3. The main part is at least approximately quadratic.

Implications to Radiation Protection

If the results for C3H 10T1/2 cells are considered to be pertinent to radiation protection, they should be expressed as transformation per cell irradiated rather than per surviving cell. This results in Figure 3. It is unlikely that experimental data obtained at high dose rate would, below about 1 Gy, be interpreted as other than a straight line which would underestimate the true value at low doses by a factor of perhaps 5. The true risk could be determined at low dose rates at doses of less than about 100 mGy. This would permit extrapolation to the much smaller doses of concern in radiation protection. The current maximum permissible annual occupational dose of neutrons is 5 mGy. A further reduction has been recommended (ICRU 1986), and an interim reduction by a factor of two has already been promulgated by ICRP (1985).

However, as already stated, the cells involved in <u>in vivo</u> carcinogenesis may have little in common with C3H 10T1/2 cells although, at least in some instances, they exhibit the same dose-rate dependence which indicates a complex dose-effect relation, particularly at high dose rates, together with initial negative curvature that results in underestimation of the low-dose hazard. Further complications from lack of autonomous response suggested by

the great variety of dose-effect relations at higher doses can only complicate matters further. While some transformation experiments with low-LET radiation suggest a dependence similar to that for high LET, there are at any rate no reasons to assume a simpler one with higher multiplicity of events in the cell.

These considerations cast serious doubt on the notion of proportionality between cancer induction and absorbed dose which, even if the unsupported assumption of autonomous response is made, would appear to hold only for very small doses especially if based on data obtained at high dose rates. It is imperative that more data be obtained at low doses. Theoretical considerations may be useful in guiding experimental design, but they can not be expected to answer the questions which they raise.

Because of the uncertain relation between <u>in vitro</u> transformation and <u>in vivo</u> carcinogenesis, it will remain essential that the latter be investigated as well. Here, too, experiments at low doses are demanding, and they may be costly. However, the problem of low-dose carcinogenesis will not be resolved unless there are major and continuing efforts by experimenters as well as theoreticians.

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FIGURE LEGEND

FIG. 1. Breast Cancer: Mortality in Nagasaki (LSS) (After BEIR III).
a) Linear plot; b) Logarithmic plot.

FIG. 2. Transformation per surviving C3H 10T1/2 cell at high and low dose rates of fission neutrons (Hill et al. 1984). Solid lines by authors. Dashed line after Rossi and Kellerer (1986).
a) Logarithmic plot; b) Linear plot.

FIG. 3. Fig. 2b corrected for cell killing (transformants per cell at risk).

FIG. 1a

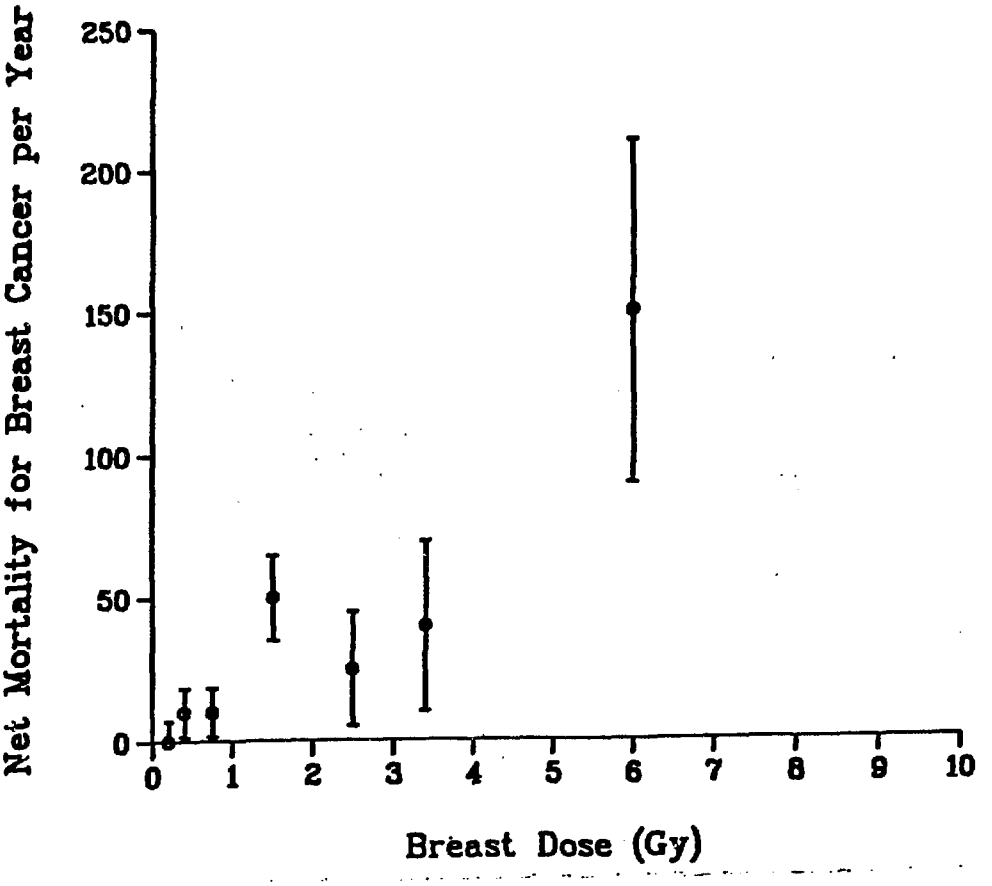

Net Mortality for Breast Cancer per Year
250
200
150
100
50
0
0
1
2
3
4
5
6
7
8
9
10
Breast Dose (Gy)

FIG. 1b

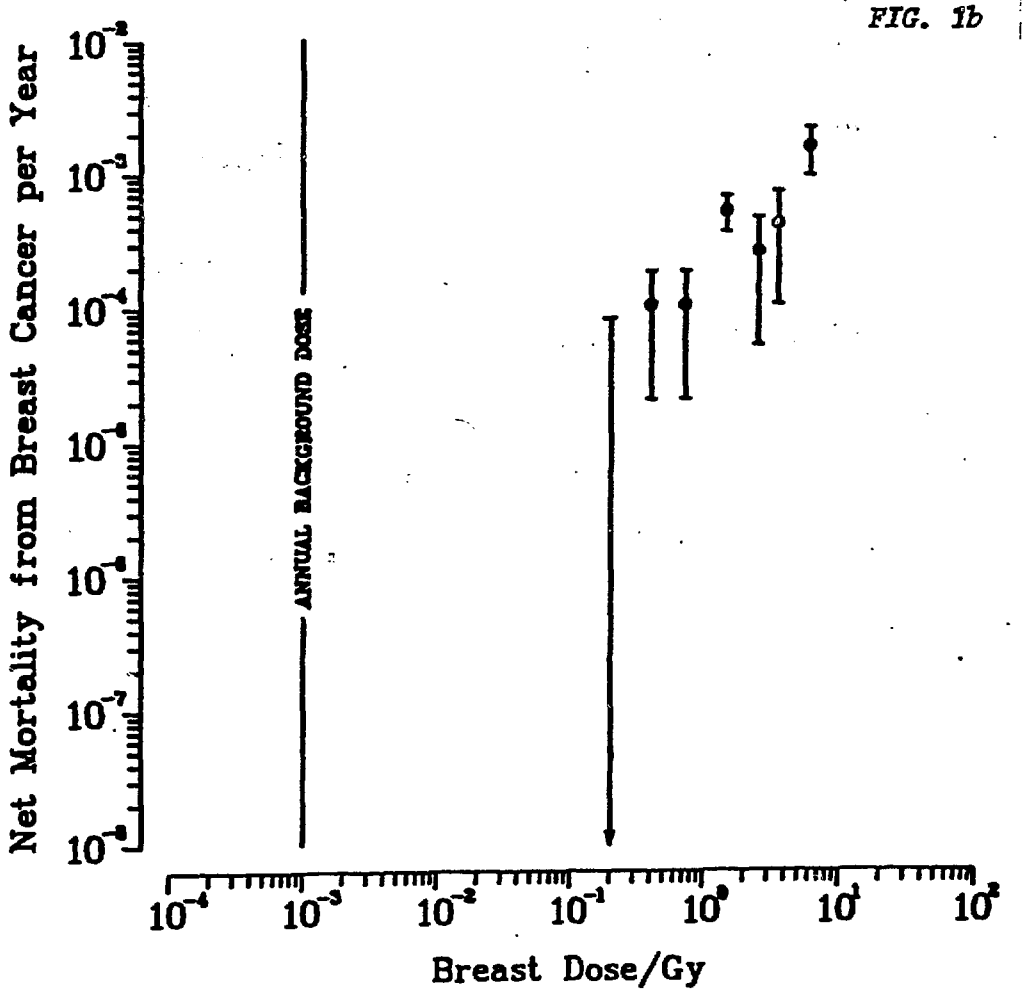

Net Mortality from Breast Cancer per Year
ANNUAL BACKGROUND DOSE
Breast Dose/Gy

FIG. 2a

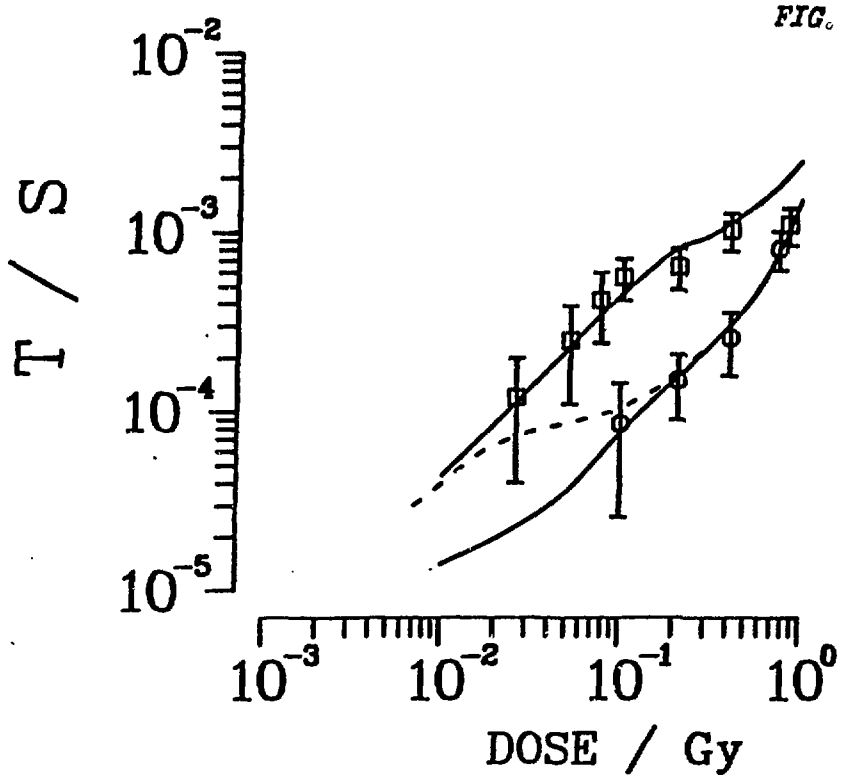
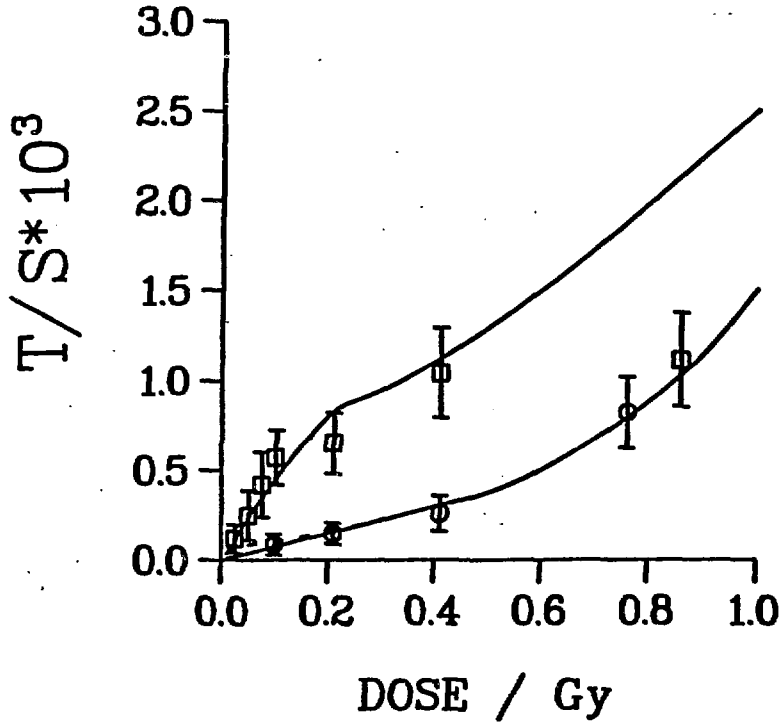

T / Ω
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-3}
10^{-2}
10^{-1}
10^{0}
DOSE / Gy

FIG. 2b


T/Ω*10³
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.0
0.2
0.4
0.6
0.8
1.0
DOSE / Gy

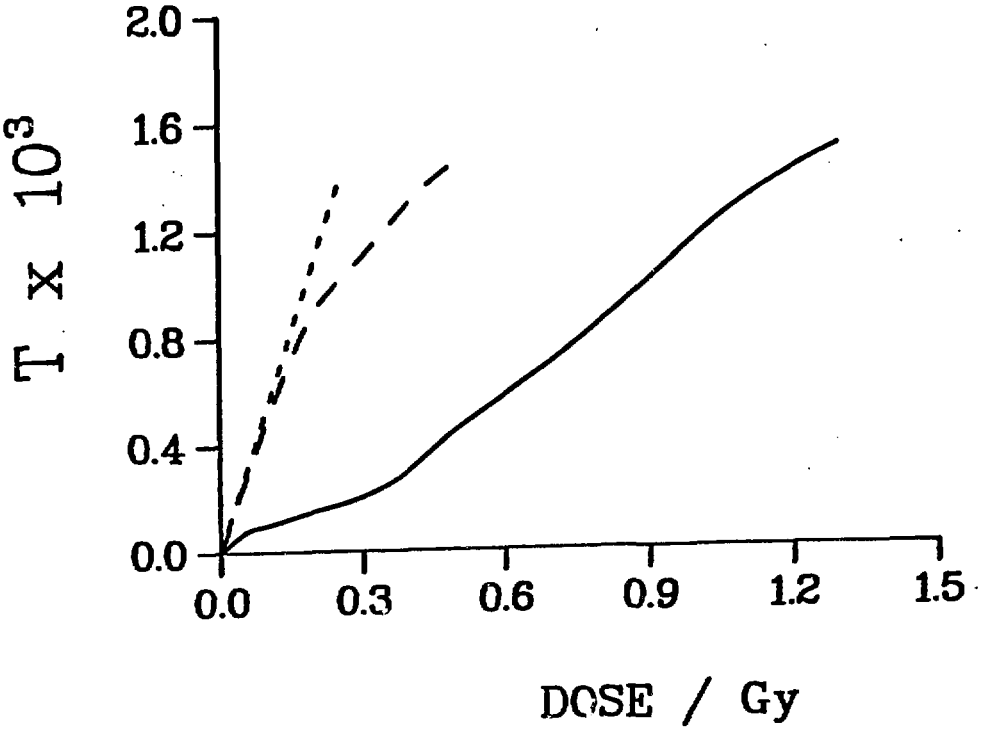


FIG. 3

DISCLAIMER