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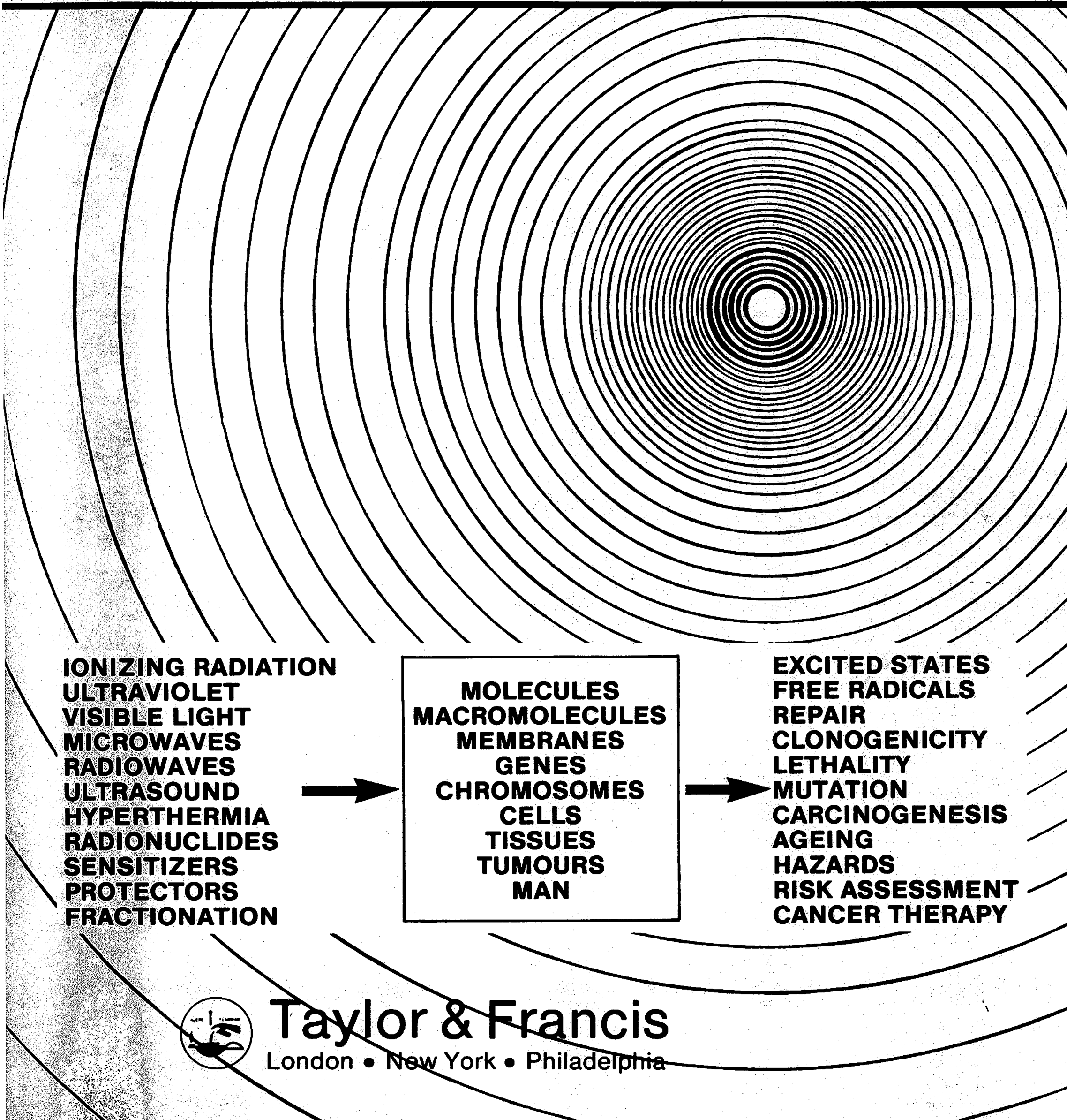

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Absence of a dose-rate effect in the transformation of C3H 10T1/2 cells by α-particles

L. HIEBER, G. PONSEL, H. ROOS, S. FENN, E. FROMKE, and A. M. KELLERER

Institut für Medizinische Strahlenkunde, Universität Würzburg, D 8700 Würzburg, FR Germany

(*Second version received 24 July 1987; accepted 14 August 1987*)

The findings of Hill *et al.* (1984) on the greatly enhanced transformation frequencies at very low dose rates of fission neutrons induced us to perform an analogous study with α-particles at comparable dose rates. Transformation frequencies were determined with γ-rays at high dose rate (0·5 Gy/min), and with α-particles at high (0·2 Gy/min) and at low dose rates (0·83–2·5 mGy/min) in the C3H 10T1/2 cell system.

α-particles were substantially more effective than γ-rays, both for cell inactivation and for neoplastic transformation at high and low dose rates. The relative biological effectiveness (RBE) for cell inactivation and for neoplastic transformation was of similar magnitude, and ranged from about 3 at an α-particle dose of 2 Gy to values of the order of 10 at 0·25 Gy. In contrast to the experiments of Hill *et al.* (1984) with fission neutrons, no increased transformation frequencies were observed when the α-particle dose was protracted over several hours.

1. Introduction

Experiments on oncogenic transformation have been performed in a variety of cell systems and with different ionizing radiations.

Extensive information has been obtained for sparsely ionizing radiations, such as γ- and x-rays, e.g. by Borek and Hall (1973), Terzaghi and Little (1976), Miller *et al.* (1979), Han *et al.* (1980), Miller and Hall (1978), and others; for densely ionizing radiation data are more limited. For α-particles results have been given by Robertson *et al.* (1983) for Balb/c 3T3 cells, and by Lloyd *et al.* (1979) and Hall and Hei (1985) for C3H 10T1/2 cells. Yang *et al.* (1985) have reported data for heavy ions of intermediate to high LET. There have also been a number of studies with neutrons (Borek *et al.* 1978, Barendsen and Gaiser 1985). Of particular importance are the results of Hill, Elkind and co-workers, who found that small doses of fission neutrons have greatly increased transformation efficiency when they are applied at low dose rates (Hill *et al.* 1984) or fractionated over several hours (Hill *et al.* 1985). The potential implications of these results and the tentative nature of attempted explanations led us to perform similar experiments with other densely ionizing radiations, and α-particles seemed to be a suitable modality that would permit highly controlled experimental conditions.

2. Materials and methods

2.1. *Cell culture and irradiation procedures*

The studies were performed with the C3H 10T1/2 mouse-embryo fibroblasts system developed by Reznikoff *et al.* (1973). Our cells were from the cell stock of Hall and Miller transfered in 1981 to the GSF, München, and kindly subcultured for us by Dr R. Trott. The cells were maintained in Eagle's basal medium supplemented with 10 per cent heat-inactivated fetal bovine serum (Biochrom, Berlin), 50 u/ml penicillin, and 50 μg/ml streptomycin (BRL, Karlsruhe). Cells of passage 12 were cultured in 75 cm^2 flasks (Falcon) and incubated in a humidified gas atmosphere (95 per cent air, 5 per cent CO_2) at 37°C. The plating efficiency of control cultures was between 20 and 30 per cent. Twenty-four hours before the exposures the cells were plated in 25 cm^2 flasks for γ-irradiation, or in special dishes consisting of a glass ring of 5 cm diameter and a foil bottom of 2 μm thickness (Hostaphan, Kalle Chemie Wiesbaden) for α-irradiation. In order to avoid settlement at the edge of the dishes where they may not be reached by the α-particles, cells were plated only in the centre area (3·8 cm diameter) with a small amount of medium (0·5 ml). Three hours later, when the cells were attached, 4·5 ml of culture medium were added. The beginning of the irradiation, both for the low dose-rate and high dose-rate experiments, was 24 ± 2 h after plating.

During the time of irradiation the cells were in exponential growth. This was verified by (a) growth curves, (b) flow-cytometry measurement of the DNA content, and (c) the determination of cells in S-phase by labelling with [^{3}H]thymidine (37 kBq/ml, 20 min).

The growth curves were exponential from about 10 to 12 h after plating, up to at least 48 h. The doubling time was about 18 h.

By flow-cytometry measurement of the DNA content the cell cycle distribution was determined at different times after plating. At 8 h, 64 per cent of the cells were in G1-, 18 per cent in S- and 18 per cent in G2 + M-phase; subsequently the fradction of G1-phase cells decreased and the fraction of S-phase cells increased. At least from 20 to 40 h, there was a constant cell-cycle distribution of 41 per cent G1-, 38 per cent S- and 21 per cent G2 + M-cells.

The labelling index increased from about 30 per cent at 4 h to 45 per cent at 15 h after plating; afterwards it remained constant at roughly 40 per cent, up to at least 40 h. The growth characteristics were equal in the flasks and the special dishes. At the beginning of the exposures the cell density was about $10^4/cm^2$.

Gamma-ray exposures were from a cobalt-60 unit at a dose rate of 0·5 Gy/min. For the α-particle exposures the cells were irradiated from an americium-241 source (a disc of 85 mm diameter with 0·37 GBq) through the bottom foil of the dishes which were positioned on the exit foil (figure 1). The highest dose rate was 0·2 Gy/min. The lower dose rates were achieved by micro-fractionation, i.e. by periodic brief opening (0·66 s) of a computer-controlled metal-disc shutter (see figure 1;6). The dose per microfraction was 2·2 mGy. For dose rates of 2·5, 1·7 and 0·83 mGy/min the fractions were separated by 50, 102, and 154 s, respectively. On the basis of measured nuclear cross-sections (mean value 250 μm^2) the frequency of α-particles traversing the cell nucleus was calculated to be about 11/Gy, i.e. one out of 40 cells was hit in its nucleus per microfraction.

The most likely energy of α-particles emerging from the bottom foil was 2·7 MeV (see figure 2), their dose mean LET was 147 keV/μm and their frequency mean 144 keV/μm. The relatively narrow energy distribution and very narrow LET-distribution was due to a high degree of collimation; the collimator of the α-irradiator has channels of length 15 mm and channel diameters of 3 mm. The track-etch diagram in figure 3 confirms the absence of obliquely incident α-particles. Figure 4 shows the enhancement of LET with increasing penetration of the α-particles into the cell. The absorbed dose is determined as the average over 2 μm depth of

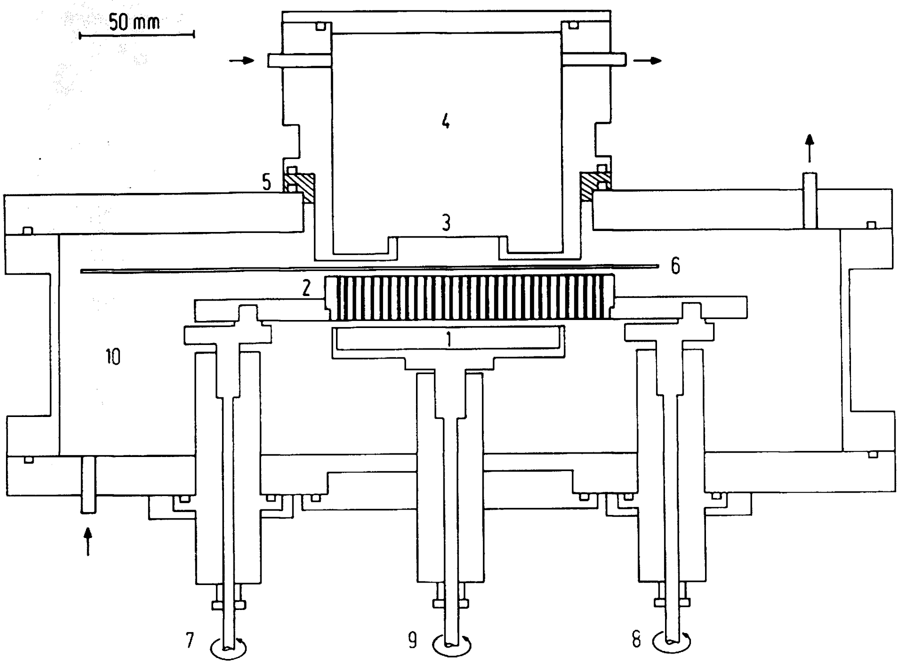

Figure 1. Diagram of the α-irradiation device: **1:** ^{241}Am Source (0·37 GBq), **2:** collimator, **3:** exit foil, **4:** incubation chamber, **5:** thermal insulator, **6:** shutter, **7,8:** wobble axes, **9:** rotating source disc, **10:** source chamber flushed with helium.

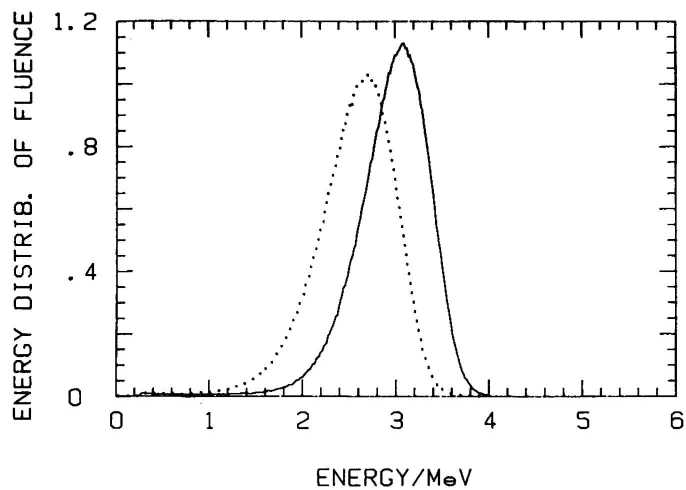

Figure 2. Measured spectra of the energy of α-particles after traversal of the exit foil (solid line) and after additional traversal of the bottom foil (Hostaphan, an equivalent of mylar) of a culture dish (dotted line).

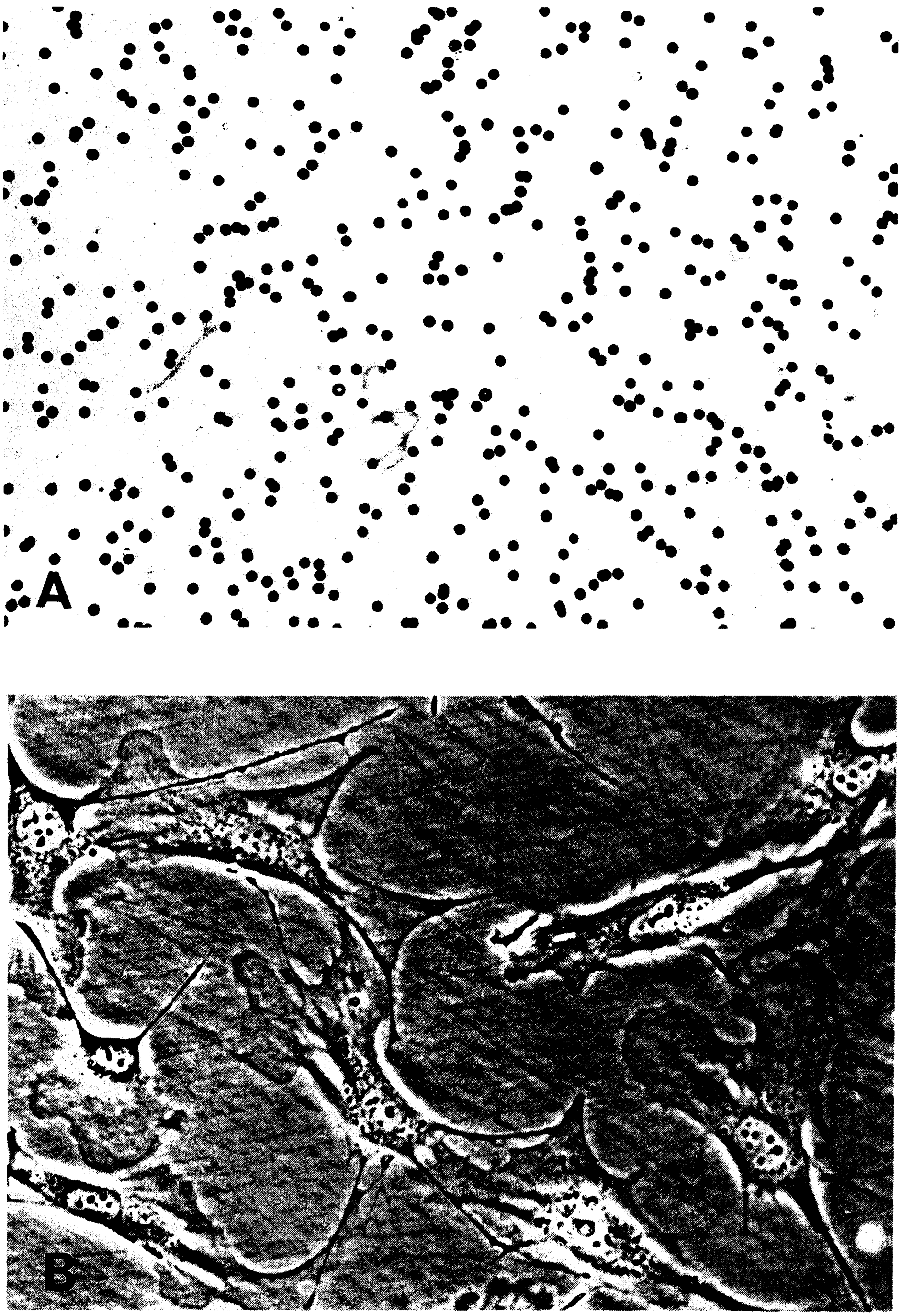

Figure 3. Comparison of C3H 10T1/2 cells at density $10^4/cm^2$ with the distribution of α-particles at a dose of 0·125 Gy.

Panel **A**: 400 μm × 275 μm field of an etched CR 39 foil exposed to an α-particle fluence of $5{\cdot}4 \times 10^5/cm^2$, corresponding to a dose of 0·125 Gy. This is calculated to correspond roughly to 1·3 α-particles per cell nucleus.

Panel **B:** 400 μm × 275 μm field with C3H 10T1/2 cells from a 24 h culture with the cell density of $10^4/cm^2$.

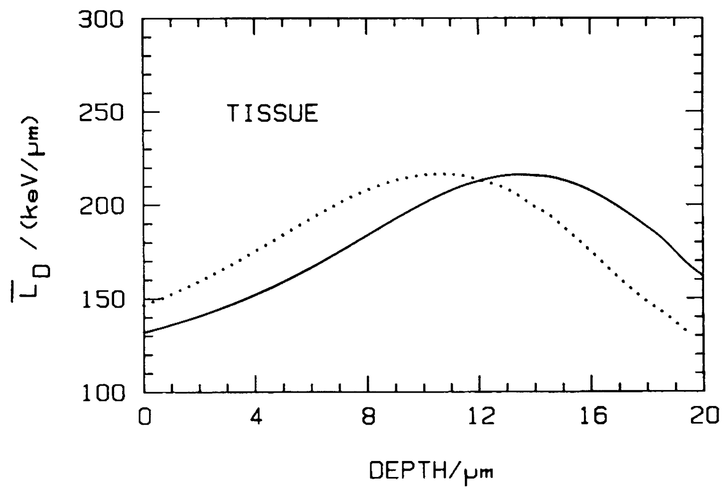

Figure 4. Dose mean LET versus depth in tissue after traversal of the exit foil (solid line) and after additional traversal of the bottom foil of a culture dish (dotted line).

penetration. The γ-ray contribution was less than 0·01 per cent of the α-particle dose.

During the exposure the cells were held in a chamber with temperature adjusted to 37°C, and with gas flow of 6 per cent CO_2 and 94 per cent air to achieve optimal pH and growth conditions. More detailed information on the α-irradiator is given elsewhere (Roos and Kellerer 1986).

2.2. *Survival and transformation assay*

After irradiation the cells were trypsinized and cell densities were determined with a Coulter Counter. If more than about 10^5 cells were necessary for the transformation and the survival assay at a specified dose—especially at higher doses—two or three dishes were irradiated successively. For the high dose-rate experiments the two or three dishes were trypsinized together and pooled. For low dose-rate experiments the cells from every dish were always plated separately. For the survival assay the numbers of plated cells were chosen to attain about 80 viable cells per 25 cm^2 flask. The flasks were incubated for 10 days. After staining with 10 per cent Giemsa, colonies with more than 50 cells were counted as survivors. For the transformation assay the cells were plated in 25 cm^2 flasks with about 300 viable cells per flask. At high doses the numbers of viable cells were lower, because of the lower surviving fraction, and not more than 20 000 cells per flask were plated in order to avoid feeder effects. The cells were incubated for 6 weeks; after an incubation time of 2 weeks, with no medium change, they reached confluency, and were then re-fed once a week. For the determination of transformed foci the cultures were washed with phosphate-buffered saline, fixed with methanol, and stained with 10 per cent Giemsa. Only foci of type 2 and 3, as described by Reznikoff *et al.* (1973), were scored as transformants.

3. Results

3.1. *Inactivation by γ-rays and α-particles*

The survival relation of C3H 10T1/2 cells after exposure to γ-rays has a pronounced shoulder (figure 5). The curve corresponds to a fit of the natural

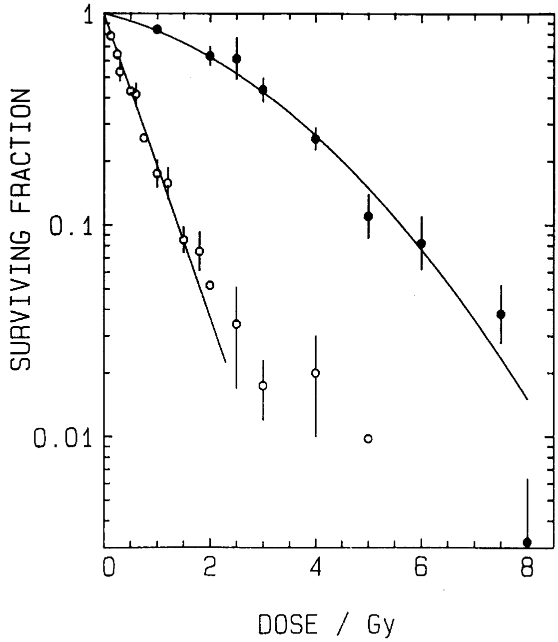

Figure 5. Inactivation of C3H 10T1/2 cells by γ-rays (closed circles) and α-particles (open circles) at high dose rates. The surviving fractions, S(D), at low dose rates are not significantly different from the fitted curve (S(0·25 Gy) = 0·61; S(0·5 Gy) = 0·39; S(0·75 Gy) = 0·25).

logarithm of survival to a linear-quadratic dependence with the coefficients $\alpha = 0{\cdot}142/\mathrm{Gy}$ and $\beta = 0{\cdot}048/\mathrm{Gy}^2$.

Inactivation by the densely ionizing α-particles follows, down to a surviving fraction of about 0·05, an exponential relation. At higher doses the surviving fraction levelled off to about 0·001. The tail of the survival curve may be due to unattached mitotic cells not reached by the α-particles.

At low dose rates there was no detectable change in survival; the data for high and low dose rates are fitted by the same relation with $\alpha = 1{\cdot}65/\mathrm{Gy}$.

3.2. *Oncogenic transformation by γ-rays and α-particles*

Table 1 shows the data for transformation after exposure to α-particles at high and low dose rates. The surviving fractions were taken from the survival relations in figure 5; for doses of 2·5 and 3·0 Gy the estimates were interpolated from observed fractions. The mean number of foci per flask was estimated from the total number, m, of foci and the number, M, of flasks:

$$\lambda = m/M \pm \sqrt{m}/M \tag{1}$$

Two flasks were assigned one focus only because their number of foci (10 and 11 at doses of 0·25 Gy and 1·0 Gy, respectively) were in evident conflict with a Poisson distribution. With this correction the dispersion, Δ (sample variance divided by the mean), was not indicative of a systematic overdispersion ($\Delta > 1$); it therefore appeared justified to base the estimates on the total number of observed foci.

However, the choice of the estimate is not critical. Table 2 gives the results based on the 'null method' of Han and Elkind (1979) which utilizes only the ratio of the

Table 1. Transformation rates after exposure of C3H 10T1/2 cells to α-particles at low and high dose rates.

$\dot{D}$ (mGy/min)	D (Gy)	S	N_s	M	m	λ	$t \pm$ SE (10^{-4})
	0	1·0	334	747	3	0·0040	0·12±0·07
200	0·125	0·81	314	172	1	0·0058	0·19±0·19
	0·25	0·66	321	369	15	0·0407	1·27±0·33
	0·5	0·44	323	384	26	0·0677	2·10±0·41
	0·75	0·29	342	239	52	0·218	6·4±0·9
	1·0	0·19	291	222	64	0·288	9·9±1·2
	1·25	0·13	353	83	21	0·253	7·2±1·6
	1·5	0·084	305	103	59	0·573	18·8±2·4
	2·0	0·037	228	121	72	0·595	26·0±3·0
	2·5	0·034	132	73	37	0·507	38·0±6·0
	3·0	0·018	81	75	34	0·453	56·0±10·0
0·83	0·25	0·66	375	264	9	0·0341	0·91±0·30
	0·5	0·44	348	16	1	0·0625	1·8±1·8
	0·75	0·29	396	131	26	0·199	5·0±1·0
1·7	0·5	0·44	343	202	14	0·0693	2·0±0·5
2·5	0·75	0·29	308	71	18	0·254	8·2±1·9

$\dot{D}$: absorbed dose rate, D: absorbed dose, S: surviving fraction (values from the fitted curve in figure 5, except at 2·5 and 3·0 Gy, where observed fractions are used), N_s: survivors per flask, M: number of flasks, m: number of foci, λ: foci per flask, t: transformation frequency per 10^4 survivors with standard error (SE).

Table 2. Transformation rates obtained from the modified estimate (equation 2).

$\dot{D}$ (mGy/min)	D (Gy)	n	Δ	λ	$t \pm$ SE (10^{-4})
	0	502	1·0	0·0040	0·12±0·07
200	0·125	171	1·0	0·0058	0·19±0·19
	0·25	354	0·96	0·0387	1·21±0·32
	0·5	358	0·94	0·0701	2·17±0·43
	0·75	195	1·13	0·204	6·0±0·9
	1·0	168	0·98	0·279	9·5±1·3
	1·25	64	0·95	0·260	7·4±1·7
	1·5	63	1·17	0·492	16·1±2·5
	2·0	71	1·14	0·685	30·0±4·0
	2·5	42	0·83	0·529	40·0±7·0
	3·0	48	1·15	0·446	55·0±11·0
0·83	0·25	255	0·97	0·0347	0·92±0·31
	0·5	15	1·0	0·0645	1·9±1·9
	0·75	106	0·89	0·212	5·3±1·1
1·7	0·5	188	0·94	0·0718	2·1±0·6
2·5	0·75	54	0·87	0·274	8·9±2·2

$\dot{D}$: absorbed dose rate, D: absorbed dose, n: number of flasks without foci, Δ: dispersion, λ: foci per flask (modified estimate), t: transformation frequency per 10^4 survivors with standard error (SE).

number, n, of flasks without foci to the total number, M, of flasks and thereby avoids any bias due to satellite colonies. These estimates, with their somewhat larger standard errors (see Balcer-Kubiczek *et al.* 1987):

$$\lambda = -\ln(n/M) \pm \sqrt{1/n - 1/M} \tag{2}$$

are in general agreement with the data in table 1.

As shown in figure 6, α-particles induce transformations substantially more effectively than γ-rays. The RBE for transformation varies from about 3 at 2·0 Gy to somewhat larger values at low doses. These RBE values are not inconsistent with the values of 2·3 to 9 obtained by Hall and Hei (1985). They are somewhat higher than values reported by Robertson *et al.* (1983) for Balb/c 3T3 cells. The γ-ray data, which were not a main objective of this study, are still subject to considerable uncertainties, and they are therefore not fitted to a numerical relation.

The results for high dose-rates of α-particles are, in figure 7, compared to those for low dose rates. There is no evidence of increased transformation frequencies at low dose rates. The broken line corresponds to a linear-quadratic relation for the number, T, of transformants per 10^4 survivors:

$$T = 0{\cdot}01 + 2{\cdot}9\, D/Gy + 5{\cdot}4\, (\mathrm{D/Gy})^2 \tag{3}$$

The solid curves permit a comparison with the results obtained for fission neutrons

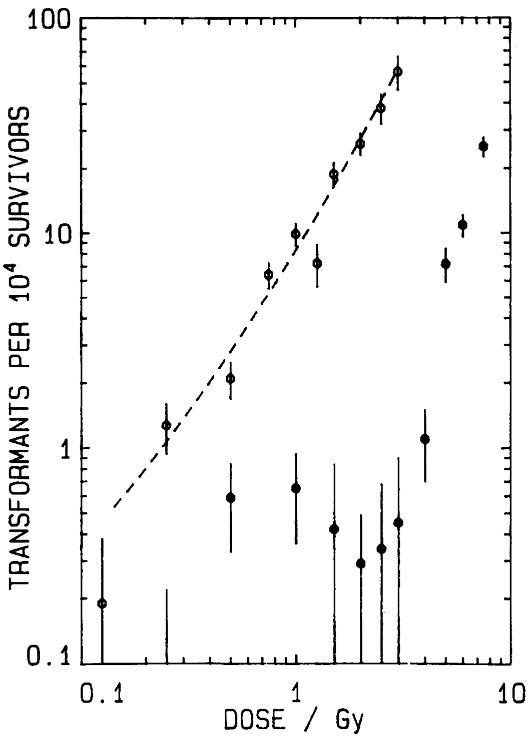

Figure 6. Transformation frequencies per surviving cells after γ- (closed circles and α-irradiation (open circles) at high- dose rates. The broken curve corresponds to equation (3).

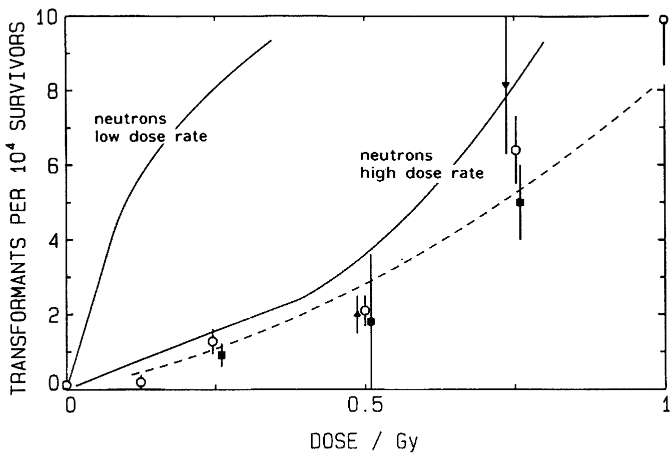

Figure 7. Transformation rates after exposure to α-particles at different dose rates: (■) 0·83 mGy/min, (▲) 1·7 mGy/min, (▼) 2·5 mGy/min, and (○) 0·2 Gy/min. The broken curve corresponds to equation (3). The solid curves represent the relations obtained by Hill *et al.* (1984) for their data at high dose rate (lower curve) and at low dose rate (upper curve) of fission neutrons.

by Hill *et al.* (1984). Their data for high dose rates (lower solid curve) are close to the dependence for α-particles. The upper solid curve represents the greatly enhanced transformation frequencies found by Hill *et al.* at low dose rate (0·86 mGy/min) of neutrons. It is evident that there is no comparable effect in the α-particle experiments.

4. Discussion

The results of Hill *et al.* (1984) were highly unexpected in view of accepted biophysical considerations (Barendsen, 1985), and they are of sufficient pragmatic importance that analogous investigations with other densely ionizing radiations are mandatory. The present study has been designed to parallel closely the experiments of Hill *et al.* (1984), so that any differences in the results would reflect differences in the effectiveness of the radiations.

Up to now there have been only tentative explanations (Rossi and Kellerer 1986, Burch and Chesters 1986, Elkind and Hill 1986) of the dose-rate effects, or of the analogous results with fractionated neutron exposures (Hill *et al.* 1985). The results for α-particles appear to exclude these explanations and there is no obvious reason why the somewhat more densely ionizing α-particles should not show, at all, a phenomenon which is so strikingly present with neutrons. Nevertheless one must note certain differences between the radiations.

Event frequencies are larger in the neutron experiments. As pointed out earlier (Rossi and Kellerer 1986), there are about six recoil particles in the nucleus of a 10T1/2 cell at a dose of 100 mGy of fission neutrons. This is substantially more than the number of about 1·1 α-particles traversing the nucleus at a dose of 100 mGy in our experiments. If, for example, the dose-rate effect were caused by a short phase in the cell cycle of greatly enhanced sensitivity (Rossi and Kellerer 1986) one would nevertheless expect to see the effect at higher α-particle doses where there are multiple events in the cell and its nucleus.

While this has not been considered in proposed models, there might be an influence of the fact that neutrons produce a more varied spectrum of moderately high and high LET than the α-particles. Furthermore it might be of importance that the range of some of the neutron recoils, and particularly the heavier recoils, are shorter than the dimensions of the cell nucleus. Another difference is that the α-exposures are virtually free of an accompanying γ-ray component, while such a component is always present with neutron irradiations. Although there is at present no evidence that a contribution of γ-rays can account for a sensitization of the cells in the low dose-rate experiments with densely ionizing radiations, we have initiated limited experiments to investigate this aspect. In one group of three experiments at low dose rate with α-particle doses of 0·25, 0·5, and 0·75 Gy a γ-contribution of about 4 per cent (from a small caesium-137 source) was applied simultanously. The observed transformation rates (with a total number of only three transformants) were insignificantly lower than those obtained in the low dose-rate experiments without the γ-component. In a further group of two experiments at α-doses of 0·25 and 0·75 Gy an equal dose of γ-rays from a cobalt-60 source was administered in six fractions during the α-exposures; the result of these combined exposures (with a total number of six transformants) was again not larger than the rates seen in the α-particle exposures at 0·25 and 0·75 Gy.

The α-particle doses were applied in multiple fractions of 2·2 mGy. However, this should be of no consequence since each of the cell nuclei experiences an α-particle in only about 1 out of 40 fractions. Even for the whole cell the number of particles per fraction is less than unity (for illustration see figure 3).

It is uncertain whether any remaining differences in the experimental procedure might contribute to the differences in the observed results. A discrepancy between our experiments and those of Hill *et al.* (1984) lies in the fact that we exposed the cells at somewhat higher densities (roughly $10^4/cm^2$), in order to obtain a sufficient number of α-irradiated cells. However, as emphasized, a number of criteria have been evaluated to ascertain that the cells were in asynchronous growth at the time of irradiation.

Hill *et al.* (1984, 1985) have pointed out that their observation are in line with certain *in vivo* studies, which indicate a similar reversed dose-rate effect for neutrons. The absence of an analogous result in our studies with α-particles must therefore not detract from the importance of the earlier studies. Instead it appears desirable to extend the investigations to other radiation modalities.

Acknowledgments

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