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MECHANISMS OF RADIATION-INDUCED NBOPLASTIC CELL TRANSFORMATION

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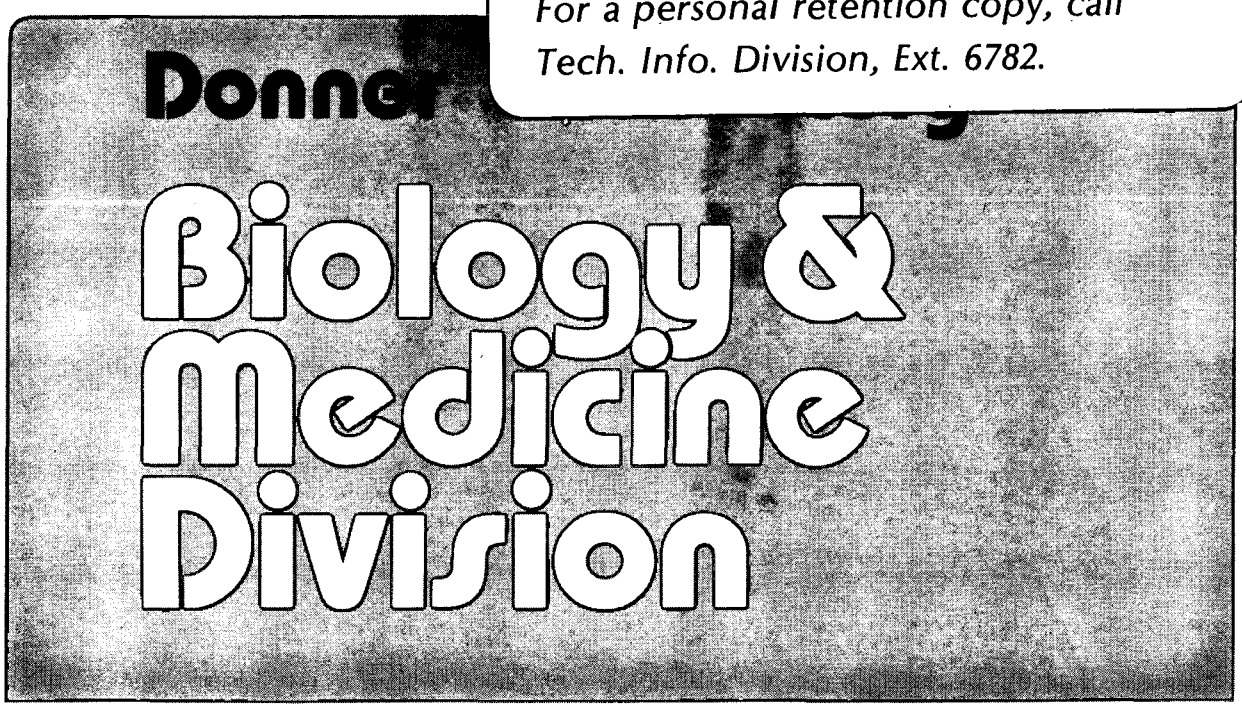

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MECHANISMS OF RADIATION-INDUCED NEOPLASTIC CELL TRANSFORMATION

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I. INTRODUCTION

In 1896, one year after the discovery of X rays, Clarance Dally, assistant to Thomas Alva Edison, may have been the first individual to develop a tumor from overexposure to X rays. He was demonstrating Edison's new invention, X-ray fluoroscopy, by exposing his arm many hundreds of times for the benefit of visitors to the Chicago World's Fair. Although the deleterious effects of X rays became known quite early during the first forty years of diagnostic radiology, quite a few physicians suffered deformaties and tumors on their hands because of repeated exposures. During the last sixty years there have been extensive studies on animals, mostly small rodents, on the long term effects of ionizing radiation, and we now know how to shield and protect ourselves.

It is generally believed that ionizing radiation can cause various types of tumors in vivo and that within a relatively low dose range the frequency of cancer generally increases with dose (Walburg, 1974). Among radiation-induced tumors, leukemia appears to have a viral etiology in certain strains of mice (Gross, 1958; Kaplan, 1967). Certain forms of leukemia in cattle also seem to have viral etiology; however, in man there is no evidence that radiation induced leukemia has viral origins, although Burkitt's lymphoma in humans may relate to Epstein-Barr virus (Rapp, 1978).

During the last fifteen years, using mammalian cell cultures as experimental models, investigators in different laboratories have demonstrated that radiation can induce neoplastic cell transformation both directly and indirectly (Borek and Sachs, 1968; Terzaghi and Little, 1975; Han and Elkind, 1979; Yang and Tobias, 1980, 1982; Stoker, 1963; Pollock and Todaro, 1968).

How radiation can induce neoplastic cell transformation both directly and indirectly is an intriguing question. Although as yet there is no clear

answer, double strand DNA breaks and cellular repair processes appear to play an important role in both radiation carcinogenesis and cocarcinogenesis. An analysis of available experimental data indicates that radiation may produce certain DNA damage (but not necessarily a single specific gene mutation) and may initiate the cell transformation directly, but that some unknown epigenetic changes may also be involved in promoting the progression and the expression of transforming properties of cells.

II. COCARCINOGENESIS: RADIATION ENHANCEMENT OF VIRAL TRANSFORMATION

The effect of radiation on the sensitivity of mammalian cells to transformation by oncogenic DNA virus has been well studied, and enhancement of viral transformation has been commonly found (Stoker, 1963; Pollock and Todaro, 1968; Lytle et al., 1970).[1] Several investigators suggested that DNA breaks, which result from X irradiation directly or from repair of UV-induced base damages, may aid viral transformation. They did not, however, specify which type(s) of DNA break, e.g., single or double strand, is the important one for the radiation enhancement effect. It has been reported that DNA double strand breaks are formed in UV irradiated human cells during repair incubation (Bradley, 1981).

The oncogene theory of carcinogenesis assumes that specific base sequences, or oncogenes, exist that can cause cancer and cell transformation.

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[1] Enhancement is the ratio of the yield of transformed cells after viruses and radiation were applied to the yield produced by virus alone. We use an operational definition for "enhancement." The enhancement ratio (E.R.) is:

$$E.R. = \frac{\text{Colonies transformed by virus + radiation}}{\text{Colonies transformed by virus alone}}$$

The DNA viruses and the RNA retroviruses carry some of the oncogenes. Indeed, it has been shown that in the course of cell transformation by viruses, the oncogenes become integrated in the mammalian cell genome. For simian virus SV 40, the oncogene sequence has been identified. It has also been shown that many copies of the oncogene may integrate into the same cell and that most of these copies do not express the transforming property. We also know that normal mammalian cells often carry several oncogenes; their presence has been proven by hybridization of DNA sequences against known oncogene DNA. Cell transformation, therefore, has genetic components; however, equally important are the gene regulatory components, which determine whether or not an oncogene is expressed.

The role of ionizing radiation in inducing oncogenic transformation is poorly understood at present. Radiation has been applied to many mammalian and human cell strains in culture. In most cases it has not produced a significant number of transformed colonies. An exception is the case of a special mouse fibroblastic strain derived from an embryo: the C3H10T1/2 strain. It is believed, however, in this case that radiation may accomplish merely the last step in a complex chain of processes that change a normal cell into a cancer cell.

Radiation can also cause point mutations in genes that may turn them into oncogenes, or bring about chromosome deletions and translocations. Radiation might bring about transposition of genes also; however, at this stage there is very little evidence that these are the pathways on which radiation acts.

Because the DNA of oncogenic viruses (SV40, for example) is double stranded and integrated into DNA of transformed cells, it seems plausible to assume that radiation-produced double-strand breaks in cellular DNA are among the main type of lesions involved in the radiation enhancement of viral

transformation. Consequently, we hypothesized that radiation can produce double-strand DNA breaks in the cell nucleus and that a misrepair of these DNA lesions enhances the integration of viral genomes and thus cell transformation. To test this hypothesis, we used a physical agent that can produce double-strand breaks efficiently; heavy ions with high linear-energy transfer (LET) have been found to induce double-strand breaks more effectively than conventional X or gamma rays (Christensen et al., 1972; Ritter et al., 1977).

At the Lawrence Berkeley Laboratory the Bevalac can accelerate heavy nuclei with atomic numbers up to 92 (uranium) to several hundred million electron volts per nucleon (MeV/u) (Alonso et al., 1982). We carried out a series of cell transformation experiments with heavy ions to test our hypothesis, and the experimental results with X rays and argon ions (570 MeV/u) are shown in Figure 1 and Table 1. The number of transformants per survivor increases rapidly with dose, and the increase of transformation frequency as a function of radiation dose is curvilinear for both argon particles and for X rays. However, the initial slope of the transformation curves are higher for heavy ions than for X rays, and it appears that at low doses single heavy ions can cause transformation. The relative biological effectiveness (RBE) for argon ions is about 1.6 to 2.1 at 300 rad, and about 3.0 at 100 rad.

Similar results were found with energetic neon particles, as reported earlier (Yang et al., 1980). Our results with other heavy ions also consistently show that high-LET radiation can be more effective than X rays in enhancing viral transformation. The RBE calculated for a single particle also increases rapidly with LET values up to 350 keV/μm, as shown in Figure 2. These data are, therefore, in agreement with the hypothesis that double-strand

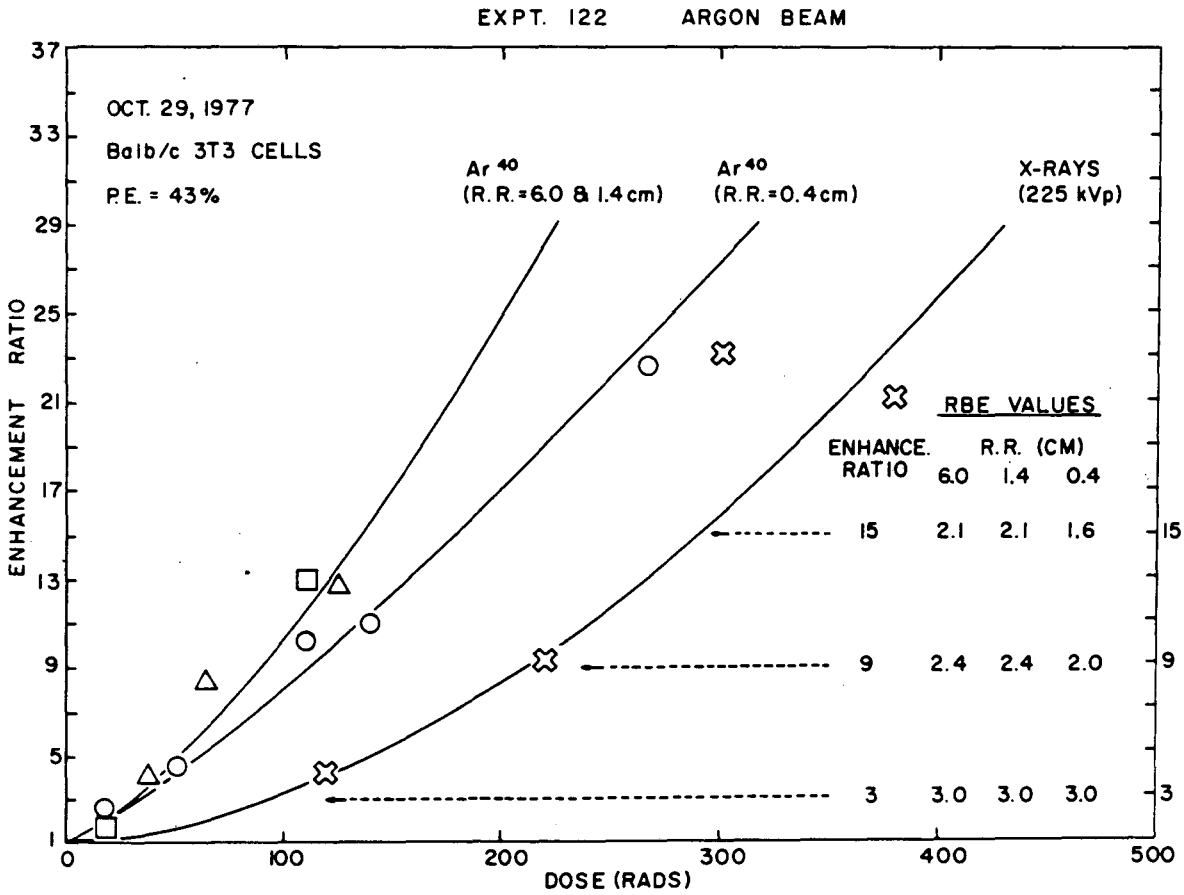


Figure 1. Enhancement effect of argon ions with various residual ranges (R.R.) and X rays on SV40 transformation of embryonic mouse cells in vitro. (XBL 785-8408)

TABLE 1. Effect of X Rays or Argon Ions on the SV-40 Viral Transformation of Cells In Vitro

Radiation	Residual Range in Water (cm)	Dose (rad)	Cells Plated per Dish	Survival (%)	Survivals per Dish	Average Number Transformants per Dish	Transformants per Survival	Enhancement Ratio
X ray	----	0	4130	43	1776	0.66	3.72×10^{-4}	1.00
(225 kVp)		120	4630	40	1852	2.50	13.50×10^{-4}	3.63
		220	6115	25	1528	5.25	34.36×10^{-4}	9.24
		360	8590	14	1202	10.38	86.36×10^{-4}	23.21
Argon ions	----	0	4898	51	2106	0.78	3.70×10^{-4}	1.00
(570 MeV/amu)	6.0	40	5055	43	2174	2.88	13.25×10^{-4}	3.56
		65	6150	34	2091	6.50	31.10×10^{-4}	8.36
		125	8914	20	1783	8.50	47.67×10^{-4}	12.81
	1.4	20	5163	45	2323	1.50	6.46×10^{-4}	1.73
		52	5685	37	2103	3.20	15.22×10^{-4}	4.09
		110	9506	24	2281	11.00	48.22×10^{-4}	12.96
	0.4	20	4850	50	2425	2.37	9.77×10^{-4}	2.63
		52	5784	41	2371	3.87	16.32×10^{-4}	4.39
		110	9388	27	2535	9.62	37.95×10^{-4}	10.20
		140	14265	20	2853	11.62	40.73×10^{-4}	10.95
		267	48446	7	3294	27.62	83.85×10^{-4}	22.54

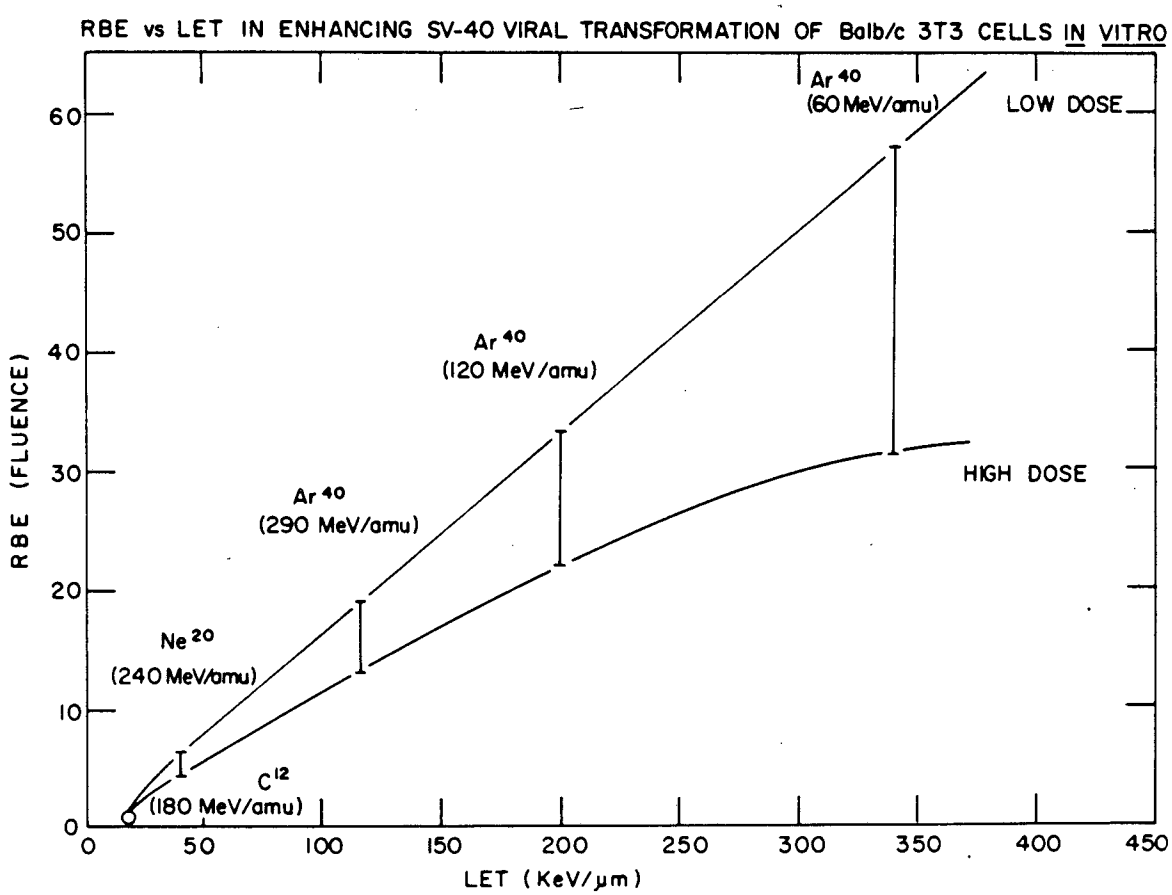


Figure 2. The relative biological effectiveness (RBE) for a single heavy particle as a function of LET in enhancing the SV40 viral transformation. (XBL 785-8399)

DNA breaks may be important lesions in enhancing cell transformation by an oncogenic DNA virus.

Some of the enhancement lesions are repairable. When the viral infection of confluent G_1 cells was delayed after X-irradiation, the transformation frequency decreased exponentially, as shown in Figure 3. An interference of repair processes with repair inhibitors, e.g., caffeine, increased the transformation frequency significantly (Figure 4). For repair inhibitor studies, cells were infected with SV40 12 hours before being exposed to X rays; right after irradiation the cells were plated into culture medium with 2 mM caffeine. One day after plating, the drug medium was replaced with fresh medium containing no drug, and the cells were fixed and stained after a 10-day and 16-day incubation for colony forming ability and transformation frequency determination respectively. Caffeine appeared to further enhance the radiation effect on viral transformation.

To date our results of heavy ion radiation experiments and repair studies appear to support the hypothesis that the enhancement of viral transformation may be due to the induction of double-strand breaks and a subsequent increase in the rate of integration of viral DNA into the DNA of the host cell. We believe that double strand breaks may act as sites for integration and proceed via misrepair of these lesions. The exact molecular mechanisms for the radiation enhancement effect is, however, still unknown and needs further study.

III. CARCINOGENIC EFFECT: NEOPLASTIC CELL TRANSFORMATION WITHOUT THE NEED FOR VIRAL INFECTION

Many investigators have studied the radiation-induced neoplastic cell transformation in vitro because the cultured cell system has the advantage of investigating malignant transformation directly at the cellular level without

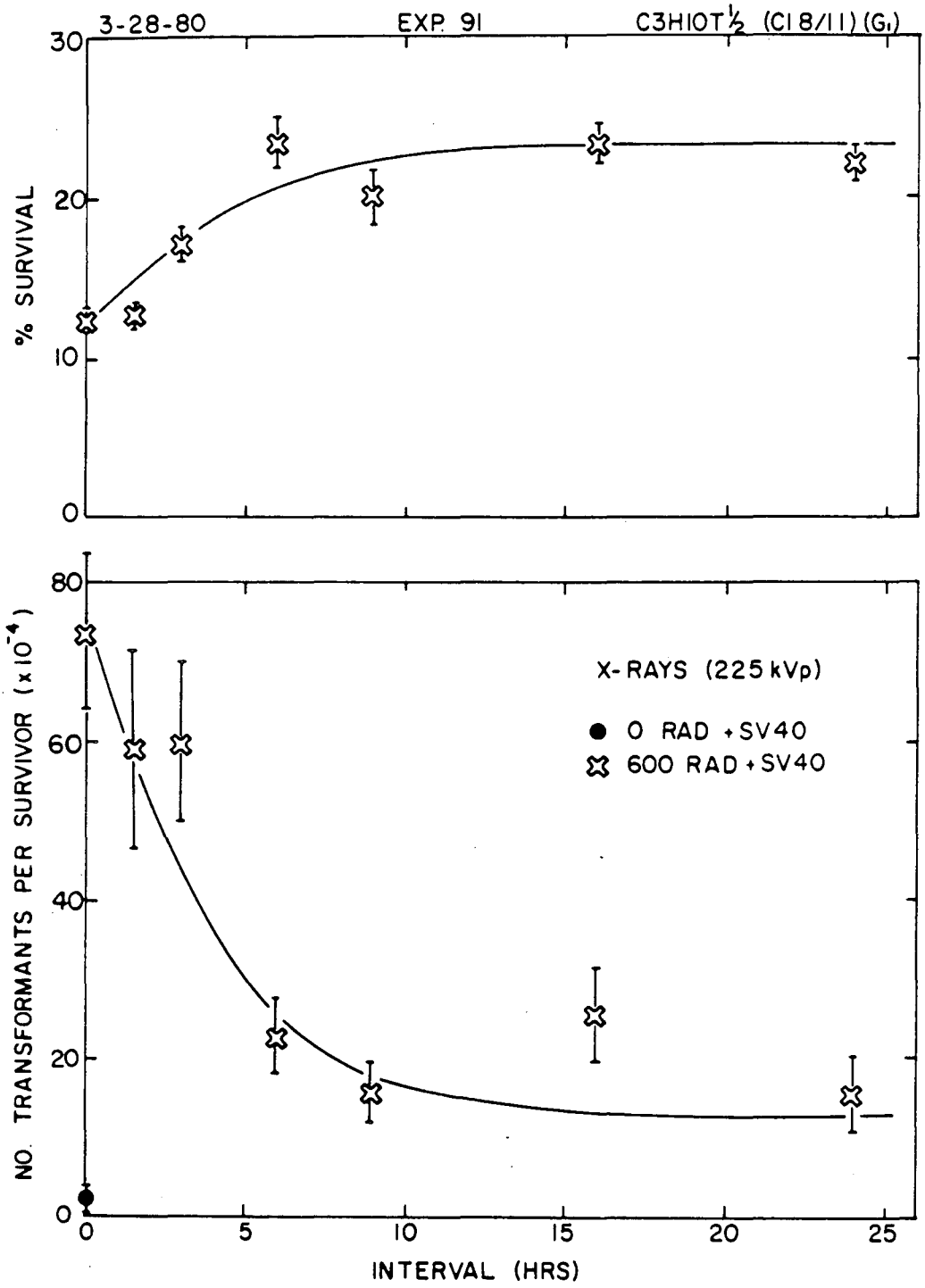


Figure 3. Kinetics of repair in confluent cells irradiated with 600 rad X rays. Top: potential lethal damage repair. Bottom: potential enhancement lesions repair. Cells were infected with SV40 at various repair intervals. (XBL 806-9830)

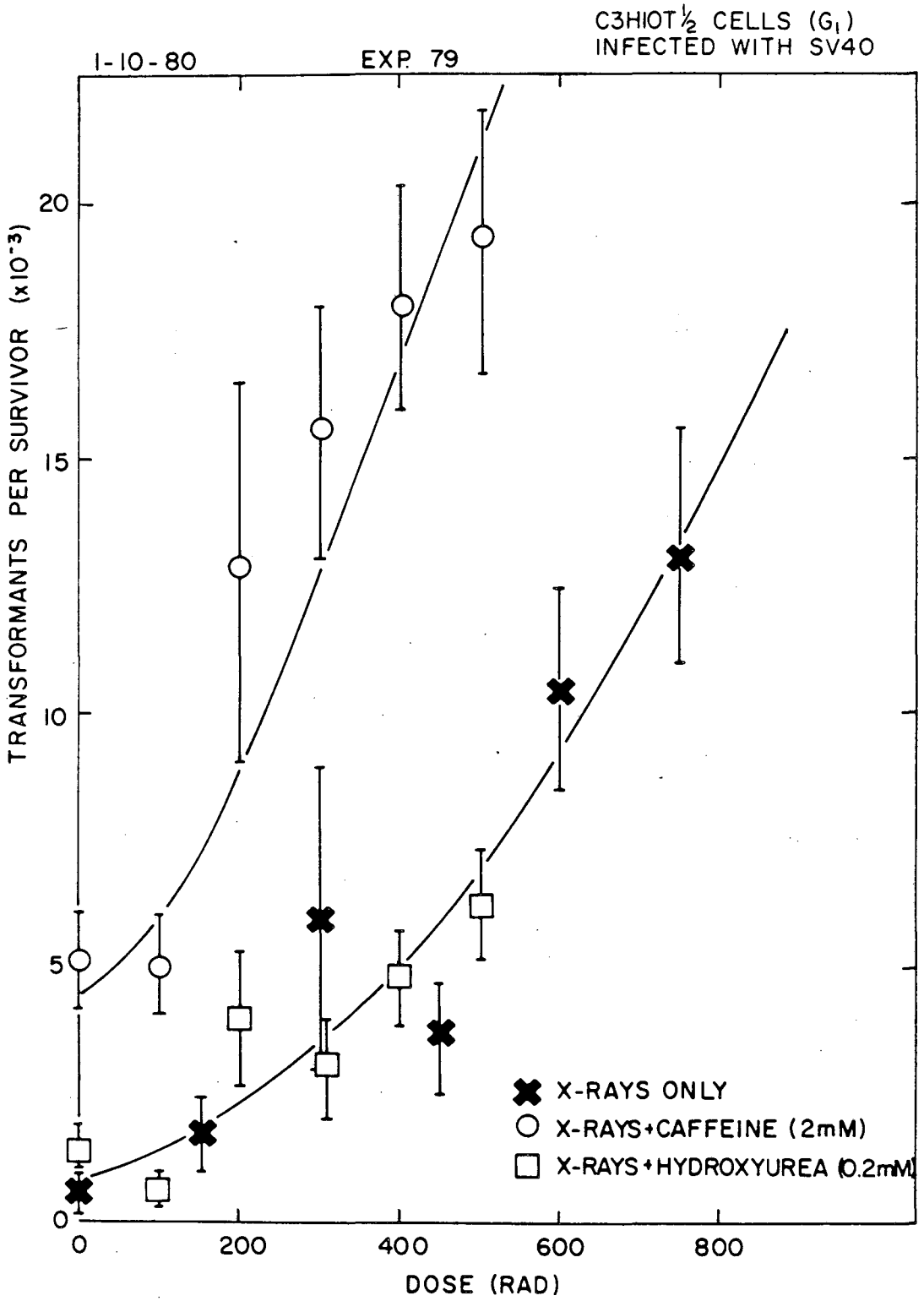


Figure 4. Effect of caffeine and hydroxyurea on the radiation enhancement of viral transformation. Cells were infected with SV40 before the irradiation and drug treatment. (XBL 806-9829)

involving the complex biological properties of the whole animal. When a population of normal cells is irradiated in vitro and allowed to proliferate at an optimal growth condition for several weeks, a small fraction of cells becomes transformed. These transformed cells can form a tumor in syngeneic test animals. Radiation can not only transform established mouse cell lines, such as C3H10T1/2 and Balb/3T3 cells, but also primary cultures of hamster embryos (Borek and Sachs, 1968). In addition to rodent cells, human fibroblasts have been transformed by X rays (Borek and Hall, 1982: Borek, 1980) and UV radiation (Maher et al., 1982; Cleaver, 1969; Setlow et al., 1969). Results obtained to date clearly demonstrate that radiation can transform mammalian cells directly.

1.0 Heavy Ion Radiation and Cell Transformation

Because of our interest in the mechanisms of radiation carcinogenesis, we have approached this problem using quantitative studies on cell transformation by heavy ions. Heavy-ion radiation can provide a wide spectrum of LET, and a variety of biological effects, e.g., cell killing, recovery kinetics, DNA breaks have shown a strong LET dependency. Consequently, a systematic study of the carcinogenesis of heavy particles can yield quantitative information that can be analyzed and compared with results of other biological effects of heavy ions to shed light on the relationships among mutation, malignant cell transformation, cell killing, repair, and DNA lesions. More insight on the mechanisms of radiation carcinogenesis may thus be gained.

Figure 5 shows the cell transformation results we obtained with energetic argon ions (330 MeV/u; LET = 140 keV/μm) and X rays. The general method we used for quantitative determination of neoplastic cell transformation in vitro is similar to that used by other investigators, except only confluent G_1 cells

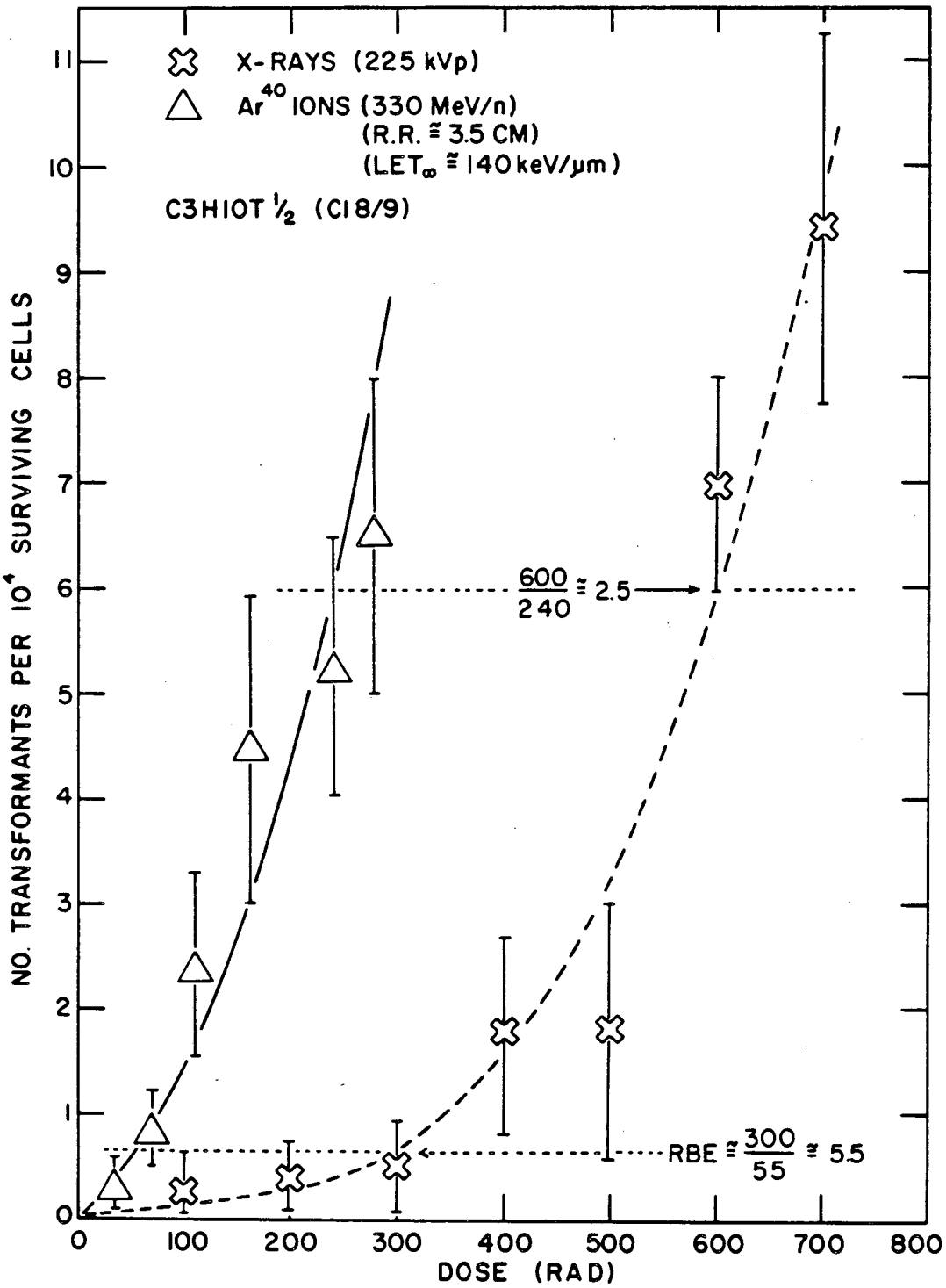


Figure 5. Induction of neoplastic cell transformation by energetic argon ions (330 MeV/u) and X rays. (XBL 835-9915)

were used for all heavy ion radiation experiments. The cell system and experimental techniques for radiation transformation study have been reported earlier (Yang and Tobias, 1982).

For both X rays and argon ions, the frequency of cell transformation per survivor increases curvilinearly with radiation dose. Argon particles, however, show a linear increase at low doses and a greater effect than X rays in inducing neoplastic cell transformation for a given dose because the number of transformants per survivor for all argon-ion doses used is consistently above the curve for X rays.

The RBE value of argon particles varies with the dose level, from about 2.5 at relative high doses to about 5.5 for low doses, below 300 rad of X rays. The effectiveness of heavy ions in inducing neoplastic cell transformation is also LET dependent. A plot of RBE as a function of LET for the various heavy ions studied in our laboratory is shown in Figure 6. The RBE is determined at the transformation frequency per survival induced by X-ray dose that kills 50% of the cells. Apparently, there is an increase of RBE with LET, at least up to about 200 keV/μm. At present we do not have data for heavy ions with LET values greater than 200 keV/μm, and we do not know at what LET value the RBE will reach its maximum. The higher RBE value for cells plated one day after irradiation is due to the fact that high LET heavy ions produce less repairable lethal and transformation lesions in the cell than X rays.

2.0 Repair of the Cell Transformation Lesion

Some of the radiation-induced transformation lesions can be repaired, and for a given dose that amount of repairable lesions formed in the cells depends on the radiation quality. When X-irradiated confluent C3H10T1/2 cells were

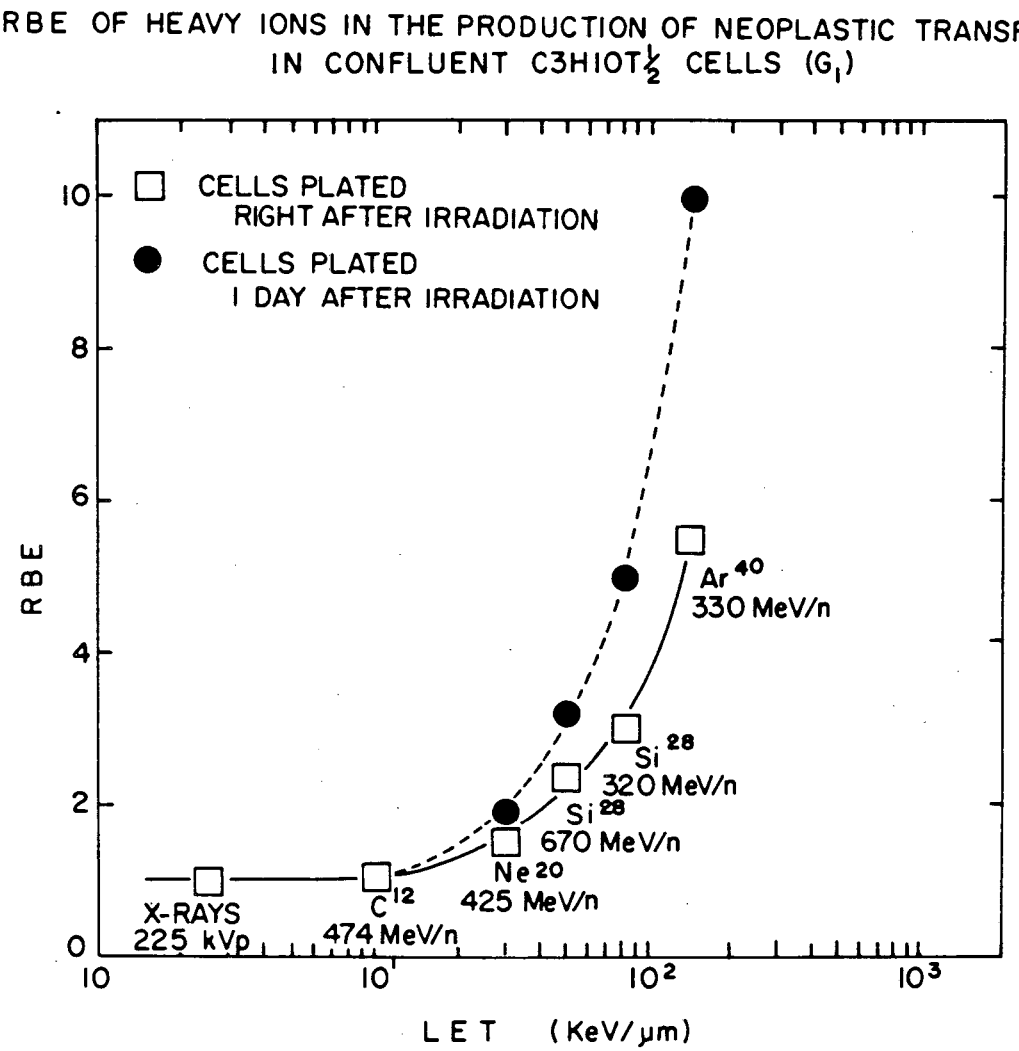


Figure 6. RBE as a function of LET of heavy ions in the production of neoplastic cell transformation. Well-confluent cells (G_1) were used for all experiments. (XBL 833-8741)

kept at 37°C for one day before being plated into dishes at a low density, the transformation frequency decreased significantly, and the dose modifying factor (DMF) was found to be about 1.6 to 1.8 (Figure 7). This decrease of transformation frequency in cells plated one day after irradiation is most likely due to the proper repair (or eurepair) of potential cell transformation lesions. An inhibition of beta DNA polymerase, which is believed to be a repair enzyme, with β-araA (adenine-β-D-arabinofuranoside) greatly enhanced the radiation transformation (Figure 8). Radiation-induced neoplastic cell transformation may, therefore, be a result of misrepair of some DNA lesions. Unlike low-LET X rays, some high-LET radiation induces very few if any repairable transformation lesions. Confluent cells irradiated with high-LET argon ions (330 MeV/u) and allowed to repair for one day at 37°C, for example, showed the same transformation frequency as cells plated immediately after irradiation (Figure 9).

3.0 Target for Neoplastic Cell Transformation

For cell killing by low and moderately high doses of ionizing radiation, nuclear DNA is an important primary target. The primary target for radiation-induced neoplastic cell transformation appears also to be the DNA. There are experimental data to suggest that radiation damage in the DNA may be the cause of neoplastic cell transformation. The first clear evidence that damaged DNA may result in neoplastic transformation came from a carcinogenesis study with fish cells (Hart and Setlow, 1975). When cells from the thyroid tissue of a fish (*Poecilia formosa*) were irradiated with UV and subsequently injected into isogenic recipients, thyroid carcinomas developed in almost all the fish. If the cells were photoreactivated immediately after UV exposure, however, very few tumors arose. This decrease of tumor incidence is due to an

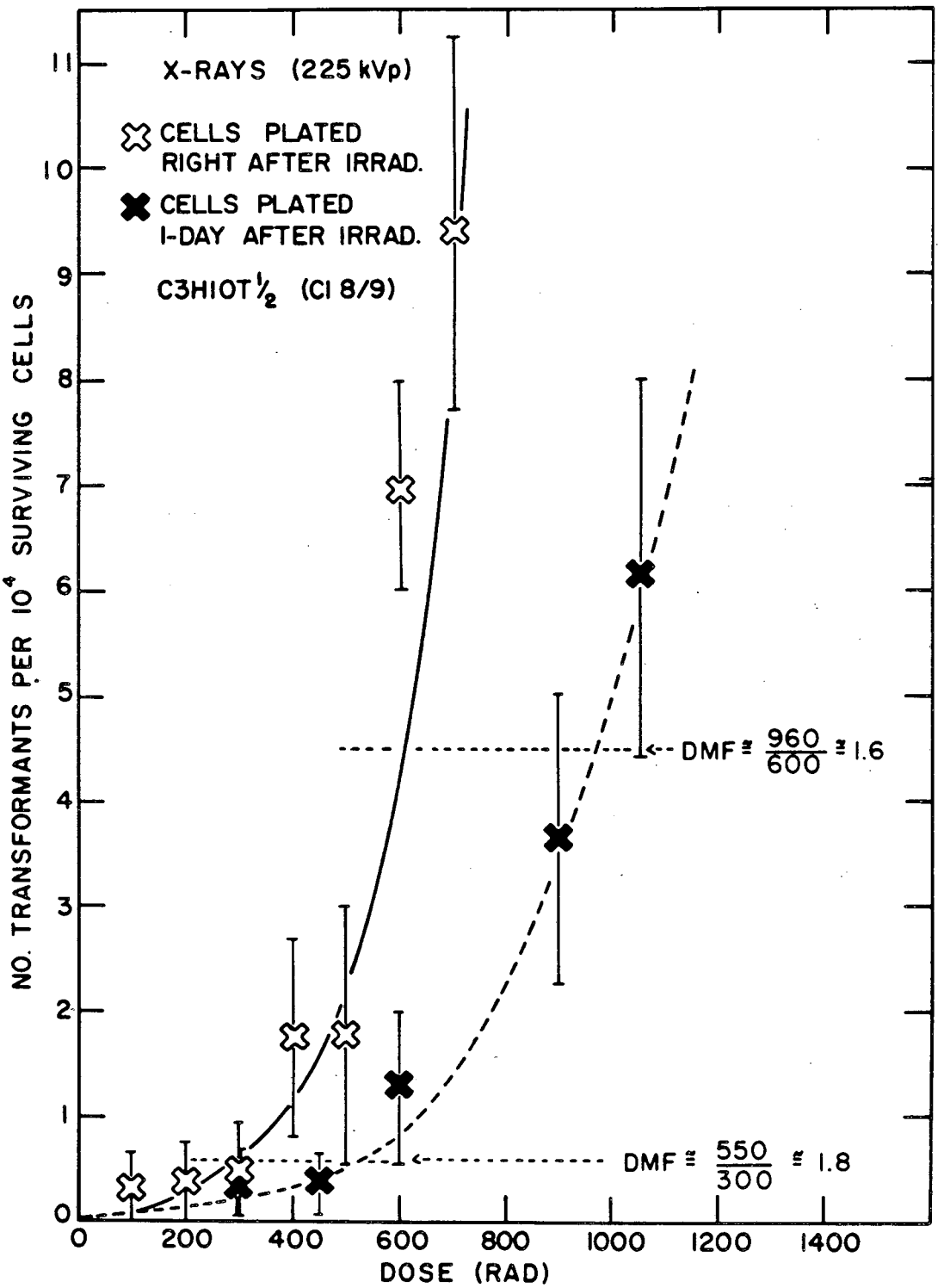


Figure 7. Repair of potential transformation lesions in X-irradiated confluent cells. (XBL 835-9914)

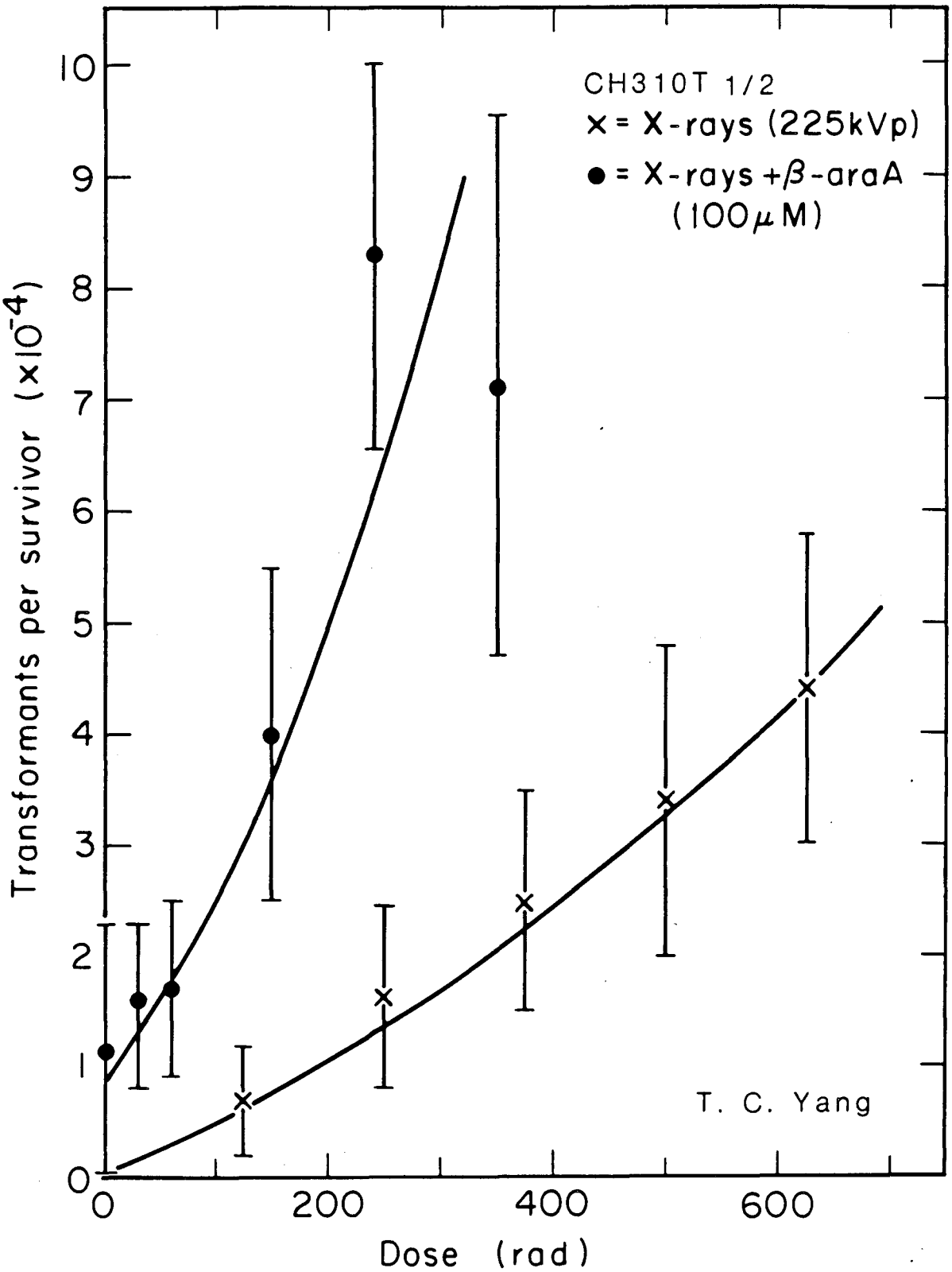


Figure 8. Enhancement of radiation-induced cell transformation by β-araA (a DNA polymerase inhibitor). (XBL 8212-4294)

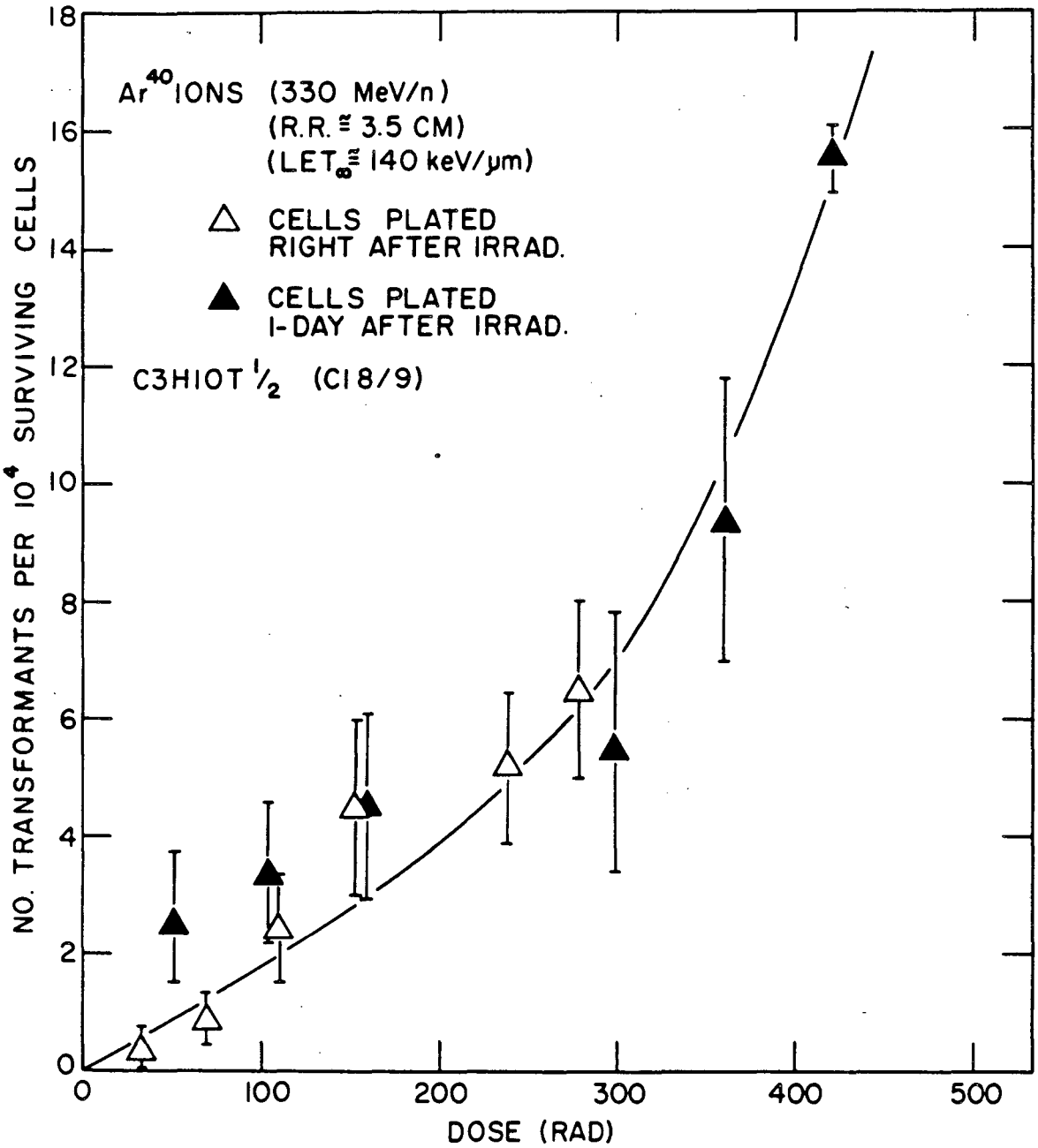


Figure 9. Effect of delayed plating on the transformation frequency of cells irradiated with energetic argon particles (330 MeV/u). (XBL 835-9951)

activation of cellular DNA repair enzymes that can remove the UV-induced DNA lesions.

The suggestion that UV-induced DNA lesions are important in neoplastic cell transformation is also supported by studies with human cells. Repair-deficient cells from patients with xeroderma pigmentosum (XP) show a higher rate of transformation than normal cells for a given UV dose (Maher et al., 1982).

Perhaps the most direct evidence suggesting DNA may be the primary target for neoplastic cell transformation is the study of malignant transformation by isotope-labelled nucleotides. Both 5-(^{125}I) iododeoxyuridine and (^{3}H) thymidine were found to induce neoplastic cell transformation effectively when incorporated into cellular DNA (LeMotte et al., 1982). At low doses, ^{125}I was over twenty-five times more effective than ^{3}H and X rays. This high efficiency in transforming mammalian cells in vitro might be due to the fact that ^{125}I radiation was highly localized to small regions of DNA at the site of each decay and produced DNA double-strand breaks. An additional evidence in favor of DNA as the target is the study with DNA analogs. Cells exposed to 5-bromodeoxyuridine at a noncarcinogenic concentration before X-irradiation gave a transformation frequency several times higher than cells treated with radiation alone (Little, 1977).

4.0 Molecular Nature of the Cell Transformation Lesion

Although experimental evidence shows that DNA is the possible primary target, we know very little about the molecular nature of the transformation lesion. The somatic cell mutation theory of cancer has been an attractive possibility, and the potential mutagenic effects of radiation have been investigated extensively. We have attempted to identify the molecular nature

of the transformation lesion by comparing the experimental data for cell transformation with that for mutation; we have concluded that neither point mutation, nor simple deletion mutation, nor sister chromatide exchange, can be the primary lesion for cell transformation.

UV radiation can induce both cell transformation and ouabain-resistant mutation (a point mutation), but no ouabain-resistant mutant in either X or heavy-ion irradiated cells has ever been found in our laboratory. Because ionizing radiation can transform cells effectively, the ouabain-resistant related "point mutation" cannot be the type of mutation lesion involved in the malignant cell transformation. Studies with XP cells suggest that sister chromatide exchange may not be the transformation lesion. XP cells, which are highly susceptible to UV radiation in neoplastic cell transformation, showed the same frequency of sister chromatid exchange as normal cells for a given UV dose (Wolff et al., 1975).

Another genetic marker used extensively for studying radiation mutagenesis in mammalian cells is the 6-thioguanine resistant (6-TG^r) mutation. The 6-TG^r mutation induced by radiation appears to be a result of DNA deletion (Cox and Masson, 1978). Heavy ions induce 6-TG^r mutation very effectively in mammalian cells, and the RBE for this mutation is about 9 at an LET range of 100 to 200 keV/μm (Cox et al., 1977). In the same LET range, however, the RBE for cell transformation is only about 5, as shown in Figure 6. An analysis of the cross section size also shows a discrepancy between 6-TG^r mutation and cell transformation. The cross section for cell transformation is about 10 to 100 times larger than that for mutation (Goodhead, 1983). In addition, it has been observed that diethylstilbestrol, a synthetic estrogen, can induce morphological and neoplastic cell transformation but not 6-thioguanine-resistant mutation (Barrett et al.,

1983). It is, therefore, difficult to equate the deletion type lesion with the transformation damage. In short, all experitmental data available at present do not support the suggestion that cell transformation arises from a simple specific radiation-induced mutation.

5.0 The Radiogenic Cell Transformation Processes

Experimental observations on the modulation of radiation cell transformation indicate that the process of neoplastic cell transformation is a complicated one and includes at least two different states: induction and expression. The results of studies using internal emitters and heavy ions suggest that some radiation-induced DNA damage may initiate the transformation. A subsequent misrepair of these DNA lesions may cause the fixation of transformation lesions, because an inhibition of repair enzymes can enhance greatly the transformation frequency.

The induction stage is a relatively short one and may be completed after one cell division. The expression stage, however, will usually take several weeks and can be modulated by various physical and chemical agents. Phorbol ester derivative 12-O-tetradecanoyl-phorbol 13-acetate (TPA), for example, when applied to cells after irradiation, promotes transformation significantly (Kennedy et al., 1978, 1980; Miller et al., 1981; Han and Elkind, 1981). Other agents reported to enhance radiogenic transformation include interferon and β-estradiol (Brouty-Boyce and Little, 1977; Borek, 1982). The expression process can also be inhibited by various chemicals, such as retinoids (Harisiadis et al., 1978; Miller et al., 1981). In our laboratory we have observed that fungizone (amphytericin B), an antibiotic for fungus, and dimethyl sulfoxide (DMSO) can decrease the frequency of cell transformation by ionizing radiation.

Figure 10 shows the effect of fungizone on radiation-induced cell transformation. Right after irradiation, the cells were incubated in growth medium with various concentrations of fungizone for 5.5 weeks at 37°C. Several well-transformed clones developed in cells irradiated with 600 rad and kept in the medium with no fungizone, but only one transformant showed in irradiated cells treated with 1.14 μg/ml fungizone. At a higher concentration of fungizone (2.27 μg/ml), no transformant was observed, suggesting an efficient inhibition of transformation. This suppression of radiation transformation by fungizone is not due to an inhibition of cell growth, because the cells treated with this antibiotic give the same number of survivors as the nontreated ones.

The inhibitory effect of amphotericin B on radiation-induced cell transformation also depends on the time of addition. Terzaghi and Little (1976) showed that mouse embryo fibroblasts X-irradiated with 300 rad give <10-4, 1.2×10^{-4} and 5×10^{-4} transformants per survivor when the fungizone was added to cells at 0, 2, and 3 weeks after seeding, respectively.

We observed a similar result with dimethyl sulfoxide (DMSO), which is shown in Figure 11. X-irradiated cells were treated for 4 weeks with DMSO medium, beginning 10 days after irradiation and plating. There is a decrease of transformation frequency with an increase of concentration of DMSO; 1% DMSO blocked the radiation transformation completely, without a significant effect on the cell growth (Figure 12).

The effect of fungizone and DMSO on the progression of cell transformation is highly interesting because both chemicals have not been found to be mutagenic at the concentration we used. Although the mechanism of progression and expression of transformation is far from understood and may be quite complicated, our studies with fungizone and DMSO indicate that some

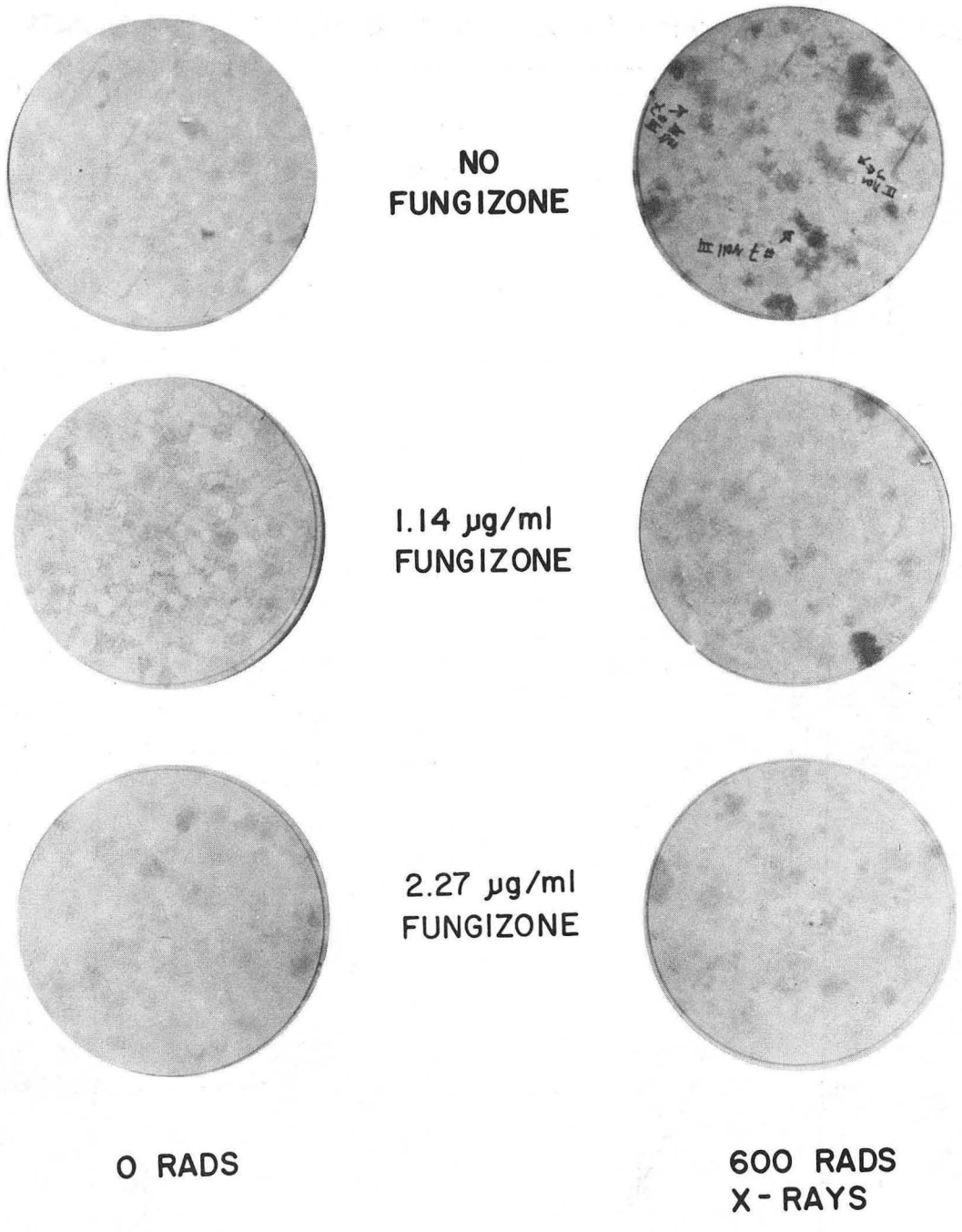


Figure 10. An inhibitory effect of fungizone on the radiation-induced cell transformation. (CBB 809-10308)

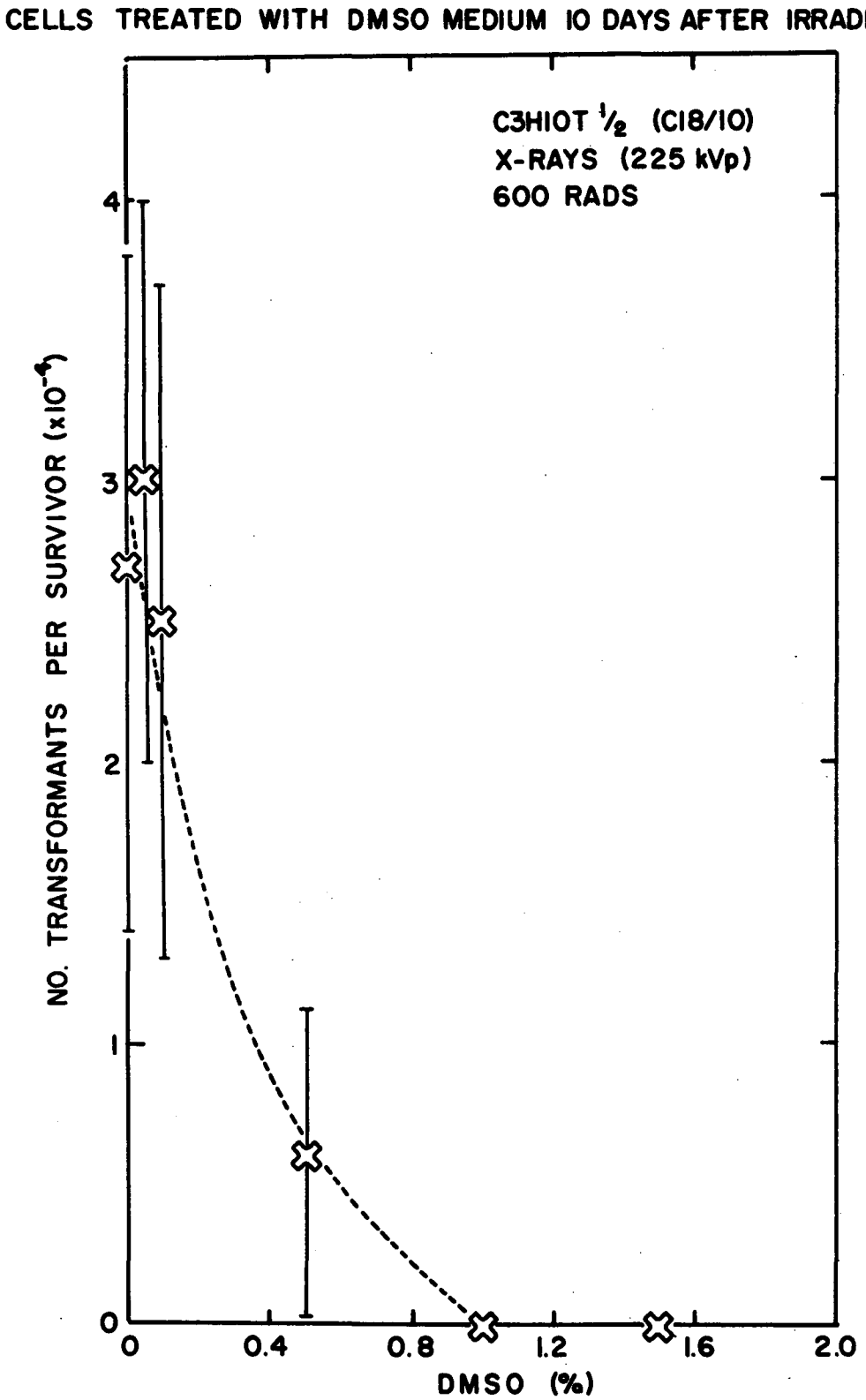


Figure 11. Effect of dimethylsulfoxide (DMSO) on the transformation frequency of cells irradiated with 600 rad X rays. Cells were treated with DMSO medium 10 days after irradiation and plating. (XBL 835-9899)

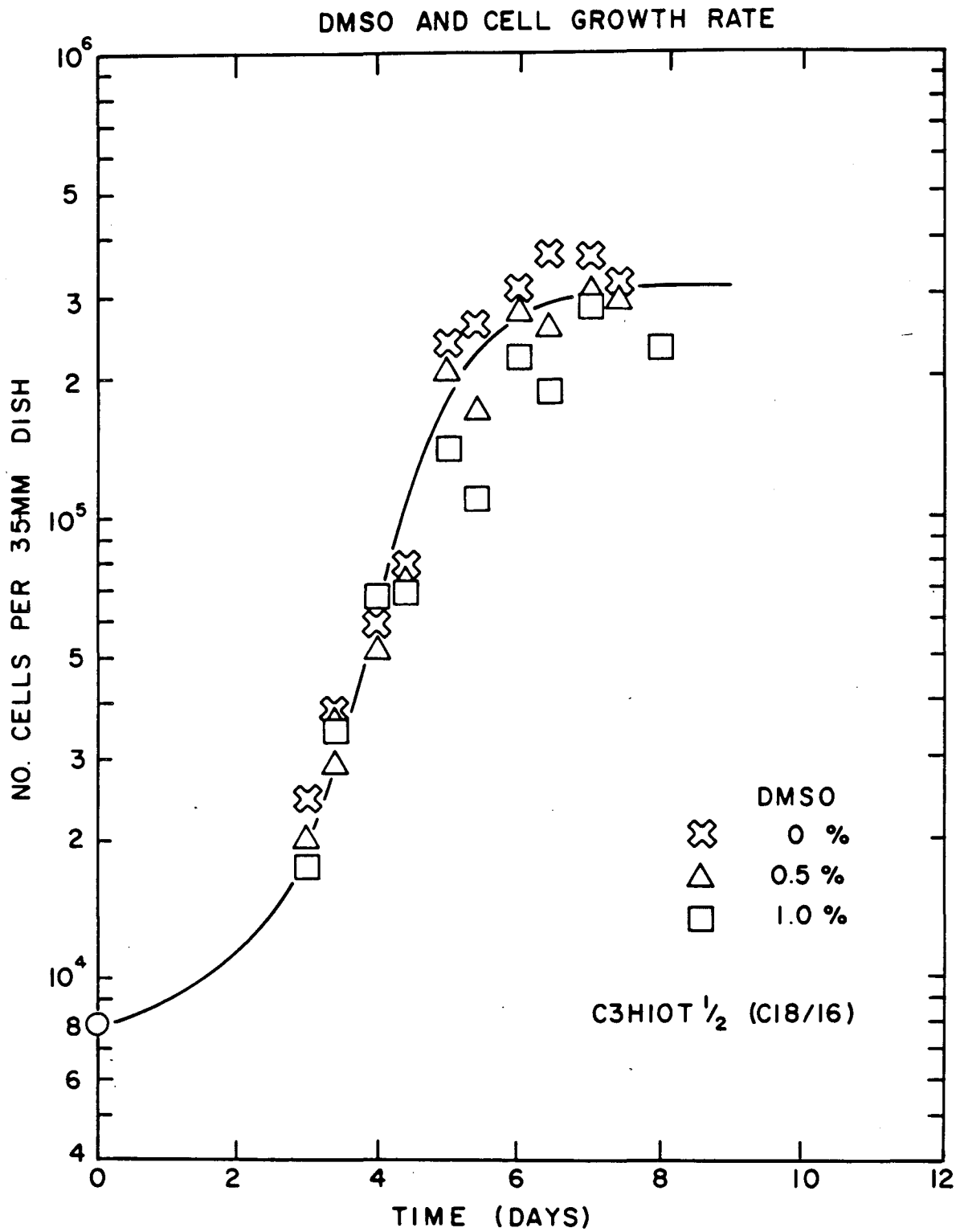


Figure 12. The growth rate of cells treated with various concentrations of DMSO. (XBL 835-9902)

nonmutagenic changes in the cell can interfere with the expression process. Some epigenetic changes, therefore, may be important and may be involved in the progression and expression processes. A simplified diagram of the possible processes of radiation cell transformation is shown in Figure 13.

Other experimental evidence, indicating that epigenetic changes can be important in the expression of tumor cell properties, is the observation of the interaction between normal and transformed cells. Unlike normal fibroblasts, which show density inhibition of growth, transformed fibroblasts tend to grow randomly and form colonies with multilayers of cells. This uninhibited growth is a prominent property of transformed fibroblasts. Recently, we have studied the effect of normal cells on the expression of transformed properties of tumorigenic cells in vitro and found that normal cells can modulate the growth of transformed cells. When well-transformed cells (10T1/2-6S), which were transformed by silicon ions and formed tumors in syngeneic hosts, were seeded into tissue culture dishes containing nontransformed cells (C3H10T1/2), the number of transformed foci decreased as the number of normal cells increased, as shown in Figure 14. We observed an average of about 130 transformed foci in the dish seeded with only 200 transformed cells (10T1/2-6S), which is a plating efficiency of about 65%, and less than 10 transformed colonies in the dish plated with 200 transformed and 6.5×10^5 nontransformed cells.

Figure 15 is a plot of the number of observable transformed foci as a function of the number of nontransformed cells plated in a 60-mm tissue culture dish. There is clearly a rapid but nonlinear decrease of transformed foci with an increase of number of nontransformed cells seeded. At present it is unknown how the normal cells modulate the growth of tumor cells and whether

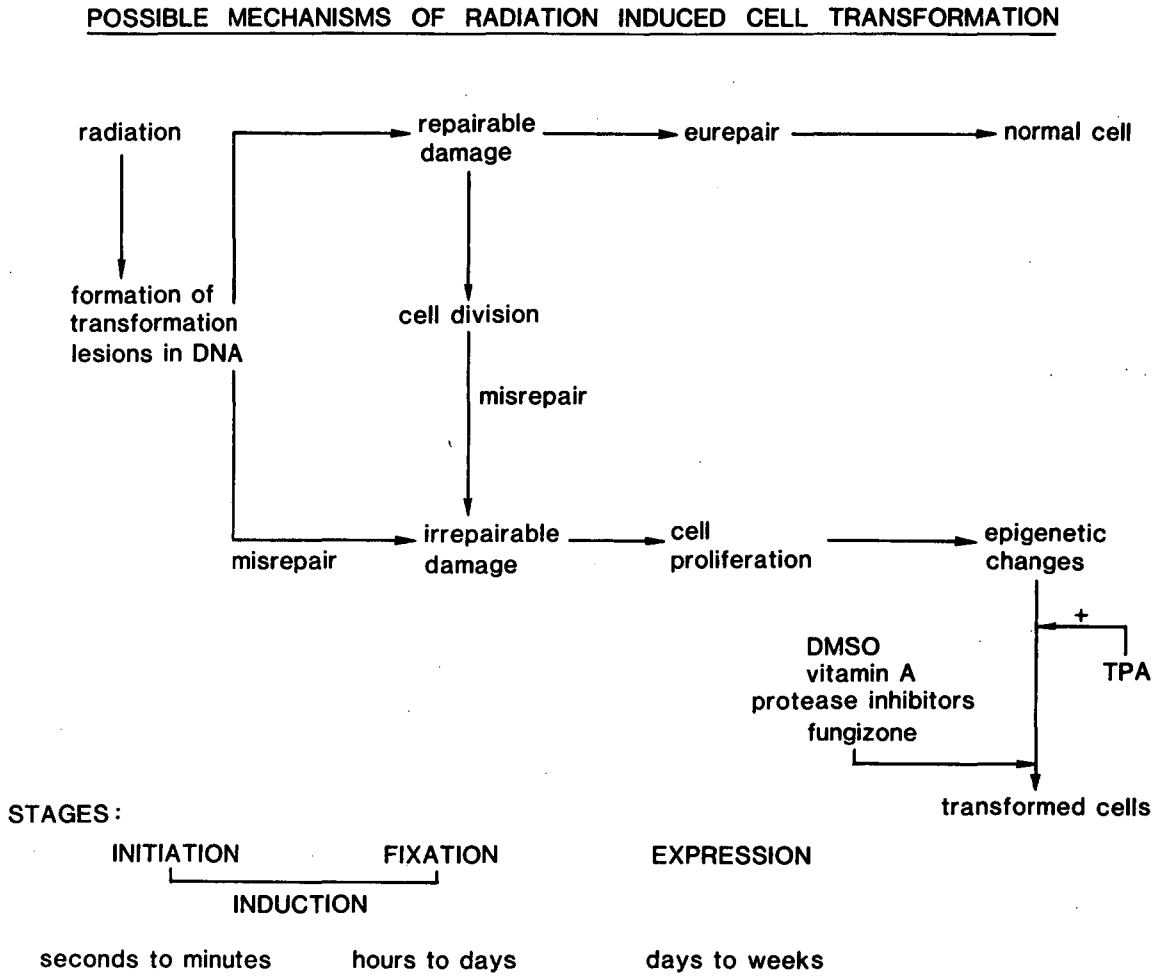
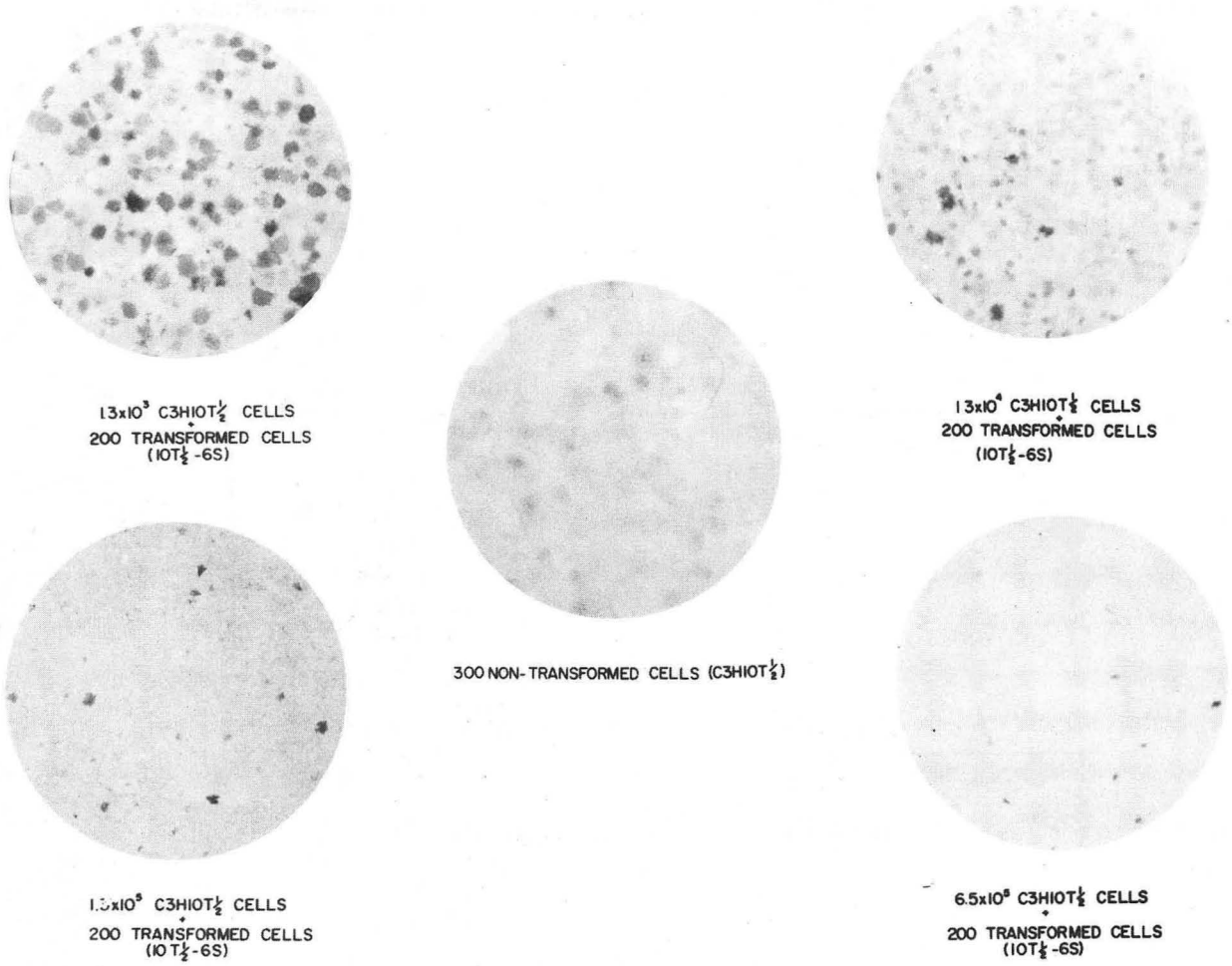


Figure 13. A schematic diagram of the possible mechanisms of radiation-induced neoplastic cell transformation. (XBL 8310-4024)

ALL DISHES INCUBATED FOR 3 WEEKS



EFFECT OF DENSITY OF NON-TRANSFORMED CELLS ON THE EXPRESSION OF TRANSFORMED CELLS

Figure 14. Effect of normal cells on the expression of tumor-cell growth property of transformed cells. Two hundred transformed cells (10T1/2-6S) were mixed with varying numbers of nontransformed cells and plated into 60-mm tissue culture dishes. Cells were incubated for three weeks at 37°C. A decrease in the number of observable transformed foci with an increase of density of nontransformed cells in the dish is evident. (CBB 833-2651)

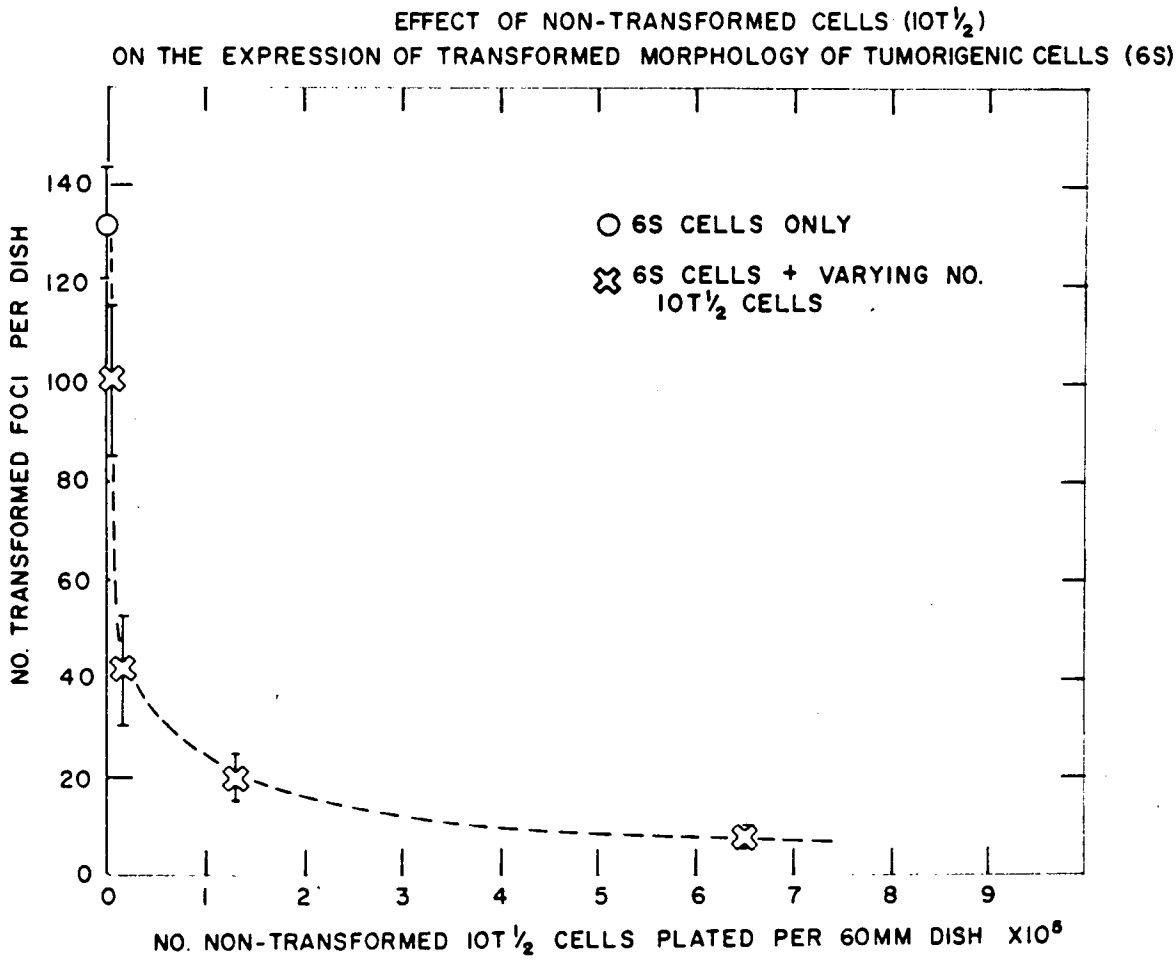


Figure 15. A plot of the number of transformed foci per dish as a function of the density of nontransformed cells. (XBL 838-11286)

this inhibition effect is irreversible. Further investigations are needed to elucidate the mechanisms of this interesting cellular phenomenon.

IV. SUMMARY

Studies with cultured mammalian cells demonstrated clearly that radiation can transform cells directly and can enhance the cell transformation by oncogenic DNA viruses. In general, high-LET heavy-ion radiation can be more effective than X and gamma rays in inducing neoplastic cell transformation. Various experimental results indicate that radiation-induced DNA damage, most likely double-strand breaks, is important for both the initiation of cell transformation and for the enhancement of viral transformation.

Some of the transformation and enhancement lesions can be repaired properly in the cell, and the amount of irrepairable lesions produced by a given dose depends on the quality of radiation. An inhibition of repair processes with chemical agents can increase the transformation frequency of cells exposed to radiation and/or oncogenic viruses, suggesting that repair mechanisms may play an important role in the radiation transformation.

The progression of radiation-transformed cells appears to be a long and complicated process that can be modulated by some nonmutagenic chemical agents, e.g., DMSO. Normal cells can inhibit the expression of transforming properties of tumorigenic cells through an as yet unknown mechanism. The progression and expression of transformation may involve some epigenetic changes in the irradiated cells.

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