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HIGH-LET RADIATION CARCINOGENESIS

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ABSTRACT

Recent results for neutron radiation-induced tumors are presented to illustrate the complexities of the dose-response curves for high-LET radiation. It is suggested that in order to derive an appropriate model for dose-response curves for the induction of tumors by high-LET radiation it is necessary to take into account dose distribution, cell killing and the susceptibility of the tissue under study. Preliminary results for the induction of Harderian gland tumors in mice exposed to various heavy ion beams are presented. The results suggest that the effectiveness of the heavy ion beams increases with increasing LET. The slopes of the dose-response curves for the different high-LET radiations decrease between 20 and 40 rads and therefore comparisons of the relative effectiveness should be made from data obtained at doses below about 20-30 rads.

INTRODUCTION

Over thirty years ago it was established that fast neutrons were more effective for the induction of tumors in experimental animals than low-LET radiations 1/ such as gamma and x-rays [1, 2, 3]. The availability of beams of different radiation qualities and increased sophistication in dosimetry has resulted in an increasing amount of quantitative data for neutron radiation-induced cancer but our understanding of the dependence of the biological effectiveness of various particles on LET has not advanced at a similar rate. The use of heavy ion beams has increased the armamentarium in attacking the intriguing questions about dose distribution, targets and cancer induction. But so far we have not been overwhelmed by revelations about the causal relationship between ionization, its density, and tumor induction. However, the precision of detecting altered gene activity, in particular of genes that may be involved in the malignant transformation of cells, by the newer molecular biological techniques added to the ability of altering ionization density appears to offer hope to the experimentalist

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A linear model has been used to describe the dose-response curve for neutron radiation-induced cancer for the purposes of protection standards. Some workers have favored a power function to describe the tumor response after exposure to high-LET radiations but it is clear that there are a number of factors that influence the response and these factors must be taken into account in the derivation of an appropriate model.

The aims of this paper are (1) to discuss the factors that recent results suggest influence the shape of the dose-response curve for cancer induction by high-LET radiation and (2) to present some preliminary results of experiments designed to investigate the relationship of LET to the effectiveness of radiation of different qualities to induce cancer. The discussions are limited to external radiation carcinogenesis.

FISSION NEUTRON CARCINOGENESIS

Most of the data for dose-response relationships for the induction of cancer by external high-LET radiation have been obtained from studies of rodents after exposure to fission neutrons [3-9]. There have also been extensive studies on the rat mammary gland with

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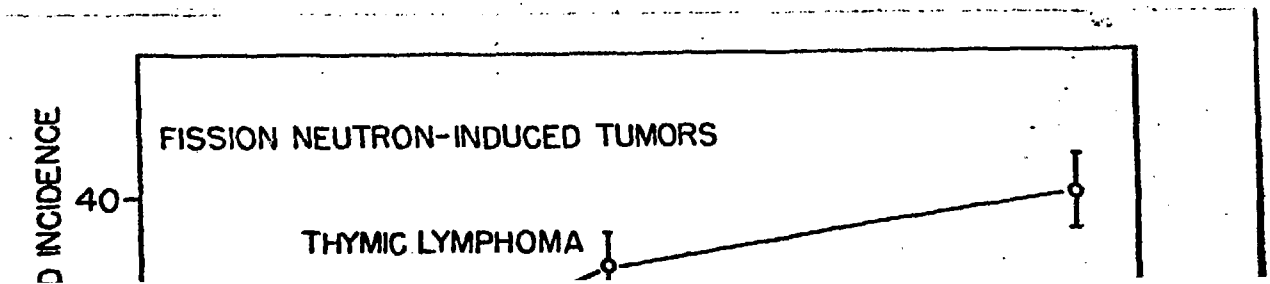
1/ The linear energy transfer (LET) is the rate of energy loss of charged particles and is usually specified in terms of kiloelectron volts per micrometer of tissue. The quantity is useful but is an average that can be measured in two ways and lacks precision.

with 430 keV neutrons [10].

Three large scale experiments on the effects of neutron radiation on life shortening have been carried out [11-13]. The studies involved a range of single doses from 5-240 rad and dose rates from 1 rad/day to 24 rad/min as well as fractionation regimes. After high dose-rate neutron irradiation of $B6CF_1$, RFM, and BALB/c mice the dose-response relationship down to about 20 rad can be described by regression of survival time on the square root of the dose. At doses below 20 rad the shape of the curve is not clear but in the case of the BALB/c data a linear fit up to a dose of 25 rad seems appropriate. The answer to the question of whether or not the initial slope is linear will make some difference to the estimate of the coefficient for the slope but will make a great difference in the explanation of the shape of the dose-response relationship. As yet the exact form of the dose-response curve for neutron-induced cancer is not known.

Rossi [14, 15] has emphasized the marked difference in the distribution of the electron tracks and the tracks of neutron secondaries. Rossi has also pointed out that at doses of 1.0 rad (10 mGy) very few nuclei in the exposed tissue are traversed by neutron secondaries. Furthermore, the number of cells traversed must increase in a proportional fashion to dose, at least up to about 25 rad (0.25 Gy) in the case of low energy neutrons [14]. It is reasonable to assume that the risk of a carcinogenic event increases with the number of cells at risk. Therefore, if the number of cells at risk was the only factor involved a linear dose response would be expected up to the dose at which all of the targets within the cells that are involved in malignant transformation are hit. At higher doses the response curve would plateau. However, with increasing doses the number of cells killed increases and the loss of cells will lead to a proportional loss of potential tumor cells [16-18]. Such a cell loss may also cause the curve for the cancer response as a function of dose to bend over as the effect per rad decreases. In the case of life shortening and tumor induction after exposure to neutrons a linearity of response appears to hold only for doses less than 20 rad and in the case of some tissues only 10 rads. It should be noted at these low doses it is impossible, with current data, to distinguish a linear from a bending curve.

It can be seen in Figure 1 that the dose-response curves for tumor induction by fission



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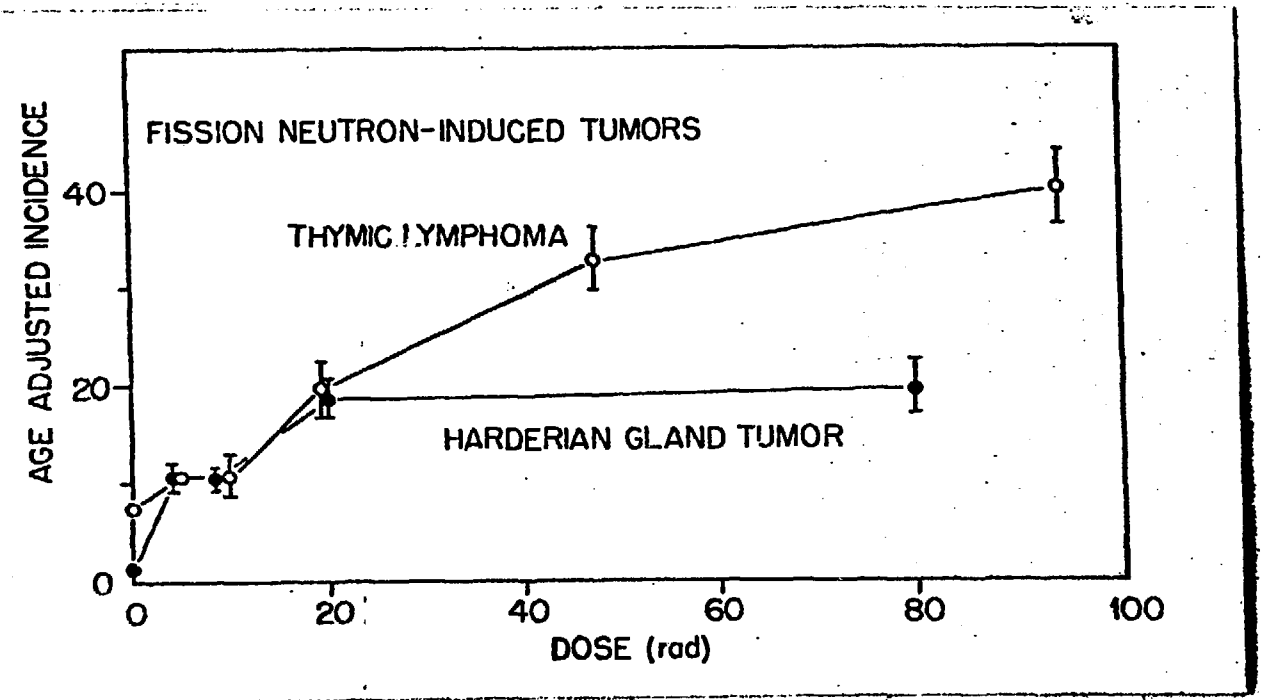


Fig. 1 Age-adjusted incidence of thymic lymphoma in RFM mice: o——o (data from ref. 5) and Harderian gland tumors in $B6CF_1$/Anl mice: ●——● (data from ref. 19) as a function of fission neutrons.

neutrons in two very different murine tissues, namely, the thymus and the gland at the back of the rodent eye described by Harder (Harderian gland), have very similar forms and appear to saturate at about 30-40 rads. Both curves show a steep initial rise, then appear to plateau between about 5-10 rad before rising again with a decreasing slope. We believe that plateau between 5-10 rad to be real as it is seen in the response of a number of tissues in female mice. A possible explanation is that in this dose-range of 5-10 rad of fission neutrons the ovary, which in the mouse is exquisitely sensitive, is ablated and the change in hormone levels and balance alters the expression of neutron-

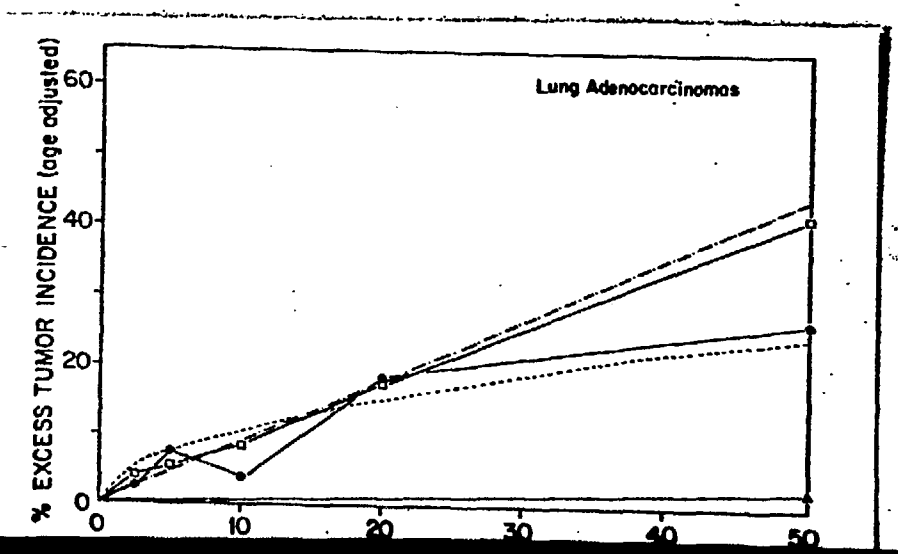
induced cell transformation. The data for males and ovariectomized mice after exposure to gamma irradiation support the role of the ovary as a factor in determining the shape of the dose-response curve.

Dose distribution, cell killing and susceptibility must all influence the shape of the curve and no model takes all of these factors into account. Since all of the dose-response curves for induction of tumors by neutron radiation show a marked decrease in slope at doses above about 30 rad estimates of the effect of low doses (below 10 rad) cannot be made from linear interpolation from data obtained at doses above about 30 rad. A model for the dose-response curve for the induction of cancer by high-LET radiation that accommodates the various factors now known to influence the response is urgently required for the estimation of risks after exposure to high-LET radiation.

FRACTIONATION AND DOSE RATE

For many years it was believed that the tumorigenic effects of neutrons, unlike low-LET radiation, were additive and lowering the dose rate or fractionating the exposures did not alter the effect. It is now clear that fractionation or protraction may enhance the effects of neutron irradiation in humans and mice [20-23]. There are not data for a sufficient number of tumor types to know whether the enhancement of effect with fractionation is a general phenomenon. A fractionated regime of 2.5 rad (25 mGy) fission neutrons (fn) over a dose range of 5-40 rads did not produce more tumors than single doses in the Harderian gland of mice [19] but in the case of lung adenocarcinomas in BALB/c/An N3d mice, 50 rad (0.5 Gy) given in two fractions separated by 30 days induced significantly more tumors than a single dose.

It can be seen in Figure 2 that the curve for the excess incidence of lung tumors as a



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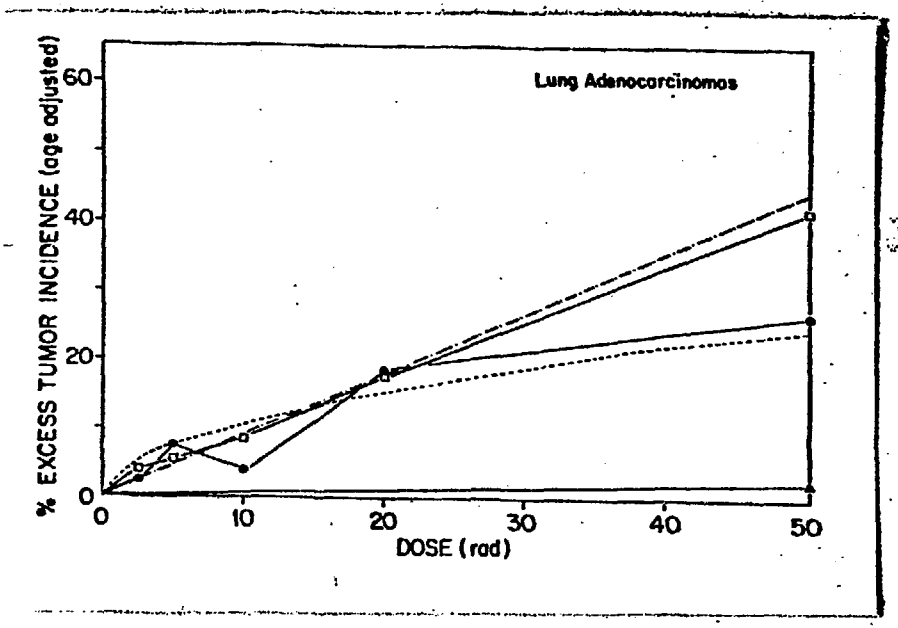
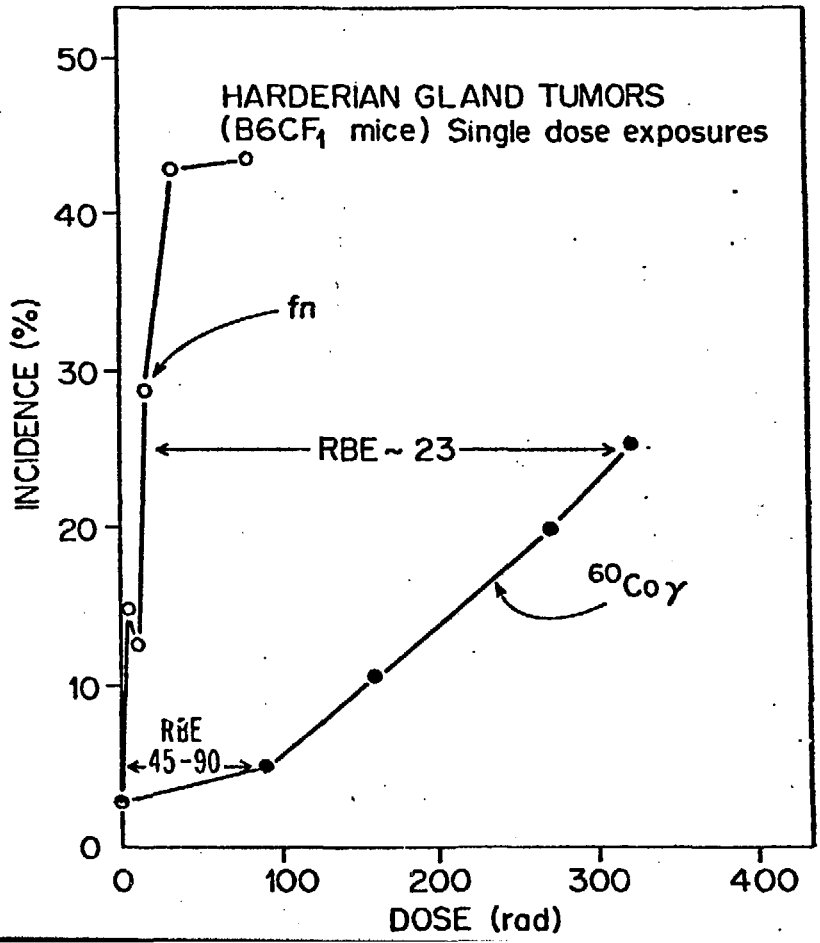


Fig. 2 Excess incidence of lung tumors as a function of total dose of fission neutrons after single exposures: ●—● and two fractions of equal doses separated by 30 days: □—□ (data from ref. 24). The response predicted from a linear regression of the data obtained for the 0-20 rad dose range of single exposures to neutrons is shown: —·—·— and also the response based on the square root of the neutron dose model: ---

function of neutron dose is approximately linear over the dose range 0-50 rad when the mice were exposed to the neutron radiation in two fractions, whereas, after single exposures the slope of the response curve decreases above 20 rad in a manner similar to that found for other tissues such as those shown in Figure 1. Since the curves for the response after single and split doses of neutrons appear to diverge only at total dose above 20 rad it seems probable that splitting the dose affects one of the factors that results in the bending over of the curve for single doses. The two factors known to influence the slope at the higher doses are dose distribution and cell killing. It seems improbable that splitting the neutron dose altered the response by changing the dose distribution in a manner that would result in more cells being transformed. We do not understand all the factors that determine the number of cells at risk but it is possible that in the interval between the two exposures to neutron radiation cell proliferation occurred to compensate for radiation induced-cell killing and at the 50 rad

dose level there was overcompensation resulting in a higher total number of cells at risk than was the case for a single exposure. An overswing in cell replacement after depletion of a proliferative population following irradiation has been documented for a number of tissues [25, 26]. It will be of interest to establish whether the increased effect of fractionating neutron exposures applies to all tissues or only to those in which cell proliferation occurs after exposure.

The relative biological effectiveness (RBE n/γ) for the induction of tumors in different tissues varies over a very wide range [19], in part, due to the marked differences in the dose-response curves for low-LET radiation. It can be seen in Figure 3 that an inverse relationship of RBE to dose results from the curvilinear response for low-LET radiation.



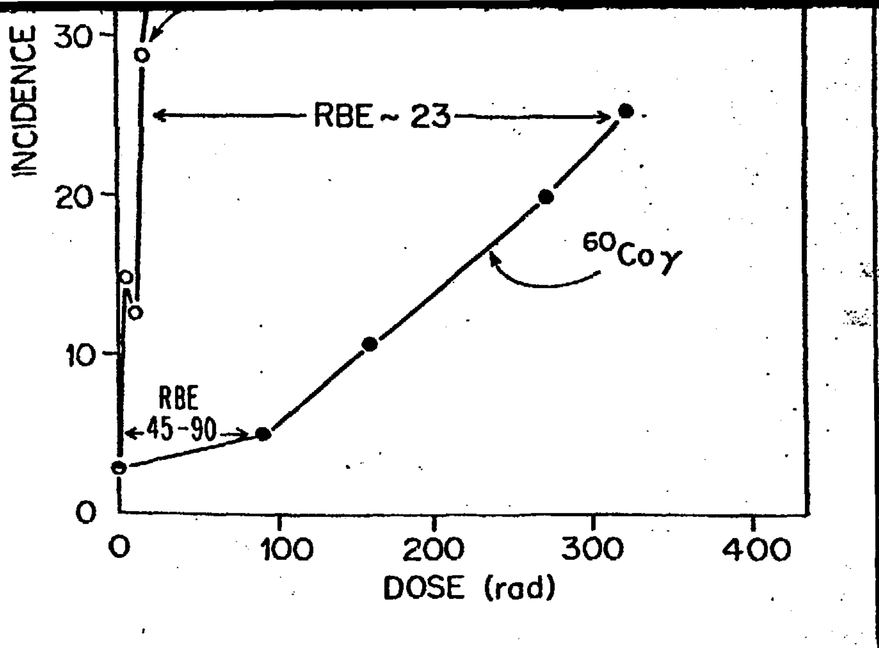


Fig. 3 Incidence of Harderian gland tumors in $B6CF_1$ mice as a function of dose of JANUS reactor fission neutrons: o—o and ^{60}Co gamma rays: •—•.

At low doses the effect per rad of low-LET radiation becomes constant, i.e. a linear response, and the value for RBE will reach a maximum. The conclusions from these observations is that the estimates of risk of cancer induction after exposure to high-LET radiation should be made directly from the dose-response relationships for cancer induction as a function of dose and not from adjusting the risk based on data obtained for low-LET radiation by the use of a Quality Factor.

THE RELATIONSHIP OF RBE TO LET

It has been found that the RBE increases for a number of endpoints as the LET increases from about 0.2 keV/μm for gamma rays to an apparent peak at about 100 keV/μm that may be obtained with certain neutrons and heavy ions [27-32]. At higher LETs the RBE decreases. There has been no systematic examination of the relationship of RBE as a function of LET for cancer induction. Since such relationships either have been or can be established for different forms of DNA damage, mutations and chromosome aberrations parallel studies of carcinogenesis have the potential of both establishing and eliminating correlations and thus winnowing the facts that are important for the understanding of the mechanisms of carcinogenesis.

We have started a comprehensive study of the influence of LET on tumor induction using

the heavy ion facilities at Lawrence Berkeley Laboratory. We have chosen as a model tumor system, the Harderian gland in mice. Although the total number of cells in these glands is small and the natural incidence is low it is reasonably susceptible to the induction of tumors by irradiation. A chance observation revealed that cells initiated by radiation could be promoted with elevated prolactin levels provided by pituitary isografts [33]. Two pituitaries from syngeneic donors, preferably from old mice, are put under the capsule of the spleen using a trocar. The transplanted isografts are not under the normal control of the hormones normally released by the hypothalamus into the portal system of the hypophysis and the transplanted pituitaries grow and release prolactin raising the amount of this hormone above normal blood levels. The elevated prolactin levels increase the amount of mammary tissue, the normal target for this hormone, and the detection of the increased mammary activity is a simple and useful indicator of the activity of the isografts. The blood levels of prolactin are variable but it is assumed that a maximum promotion effect occurs with levels that cause increase in the mammary gland tissue. It has been found that the enhancement by prolactin is equally effective whether the isografts are made after or before the irradiation. The use of pituitary isografts has two advantages. First, the tumors appear earlier than without the isografts, thus shortening the length of the experiment and second, the elevated prolactin level appears to maximize the expression of the induced lesions, thus increasing the response and reducing the number of animals required to obtain significant increases above control incidences. If, as we assume, the pituitary isografts maximize the expression of the transformed cells then the dose-response curves obtained under these experimental conditions should reflect the dose-response relationships for initiation of the cancer process. It is the comparative effectiveness of the various heavy ion beams for initiation that is of particular interest. A further advantage of this model tumor system is that we have data for tumor incidences following exposure to different energy neutrons at the JANUS reactor and the FERMI facilities [34].

The effects of helium, carbon, neon, argon, iron ion beams and ^{60}Co gamma radiation have been compared. The helium ions were produced by the Berkeley 184-in synchrocyclotron and the other ions on the BEVALAC. The BEVALAC is a high-energy heavy-ion accelerator complex in which ions are first accelerated in HILAC, a heavy-ion linear accelerator, and then injected into BEVATRON, a proton synchroton. Details of both the 184-in synchrotron and the BEVALAC and the dosimetry employed have been reported [35]. The distribution of dose in tissue from heavy charged particle beams is complex. The dose is relatively constant up to a depth in the tissue, that is dependent on the radiation quality, and then rises to a well-defined maximum known as the Bragg peak near the end of the particle track. The Bragg peaks are only a few millimeters in width and are unsuitable for the dose distribution required in our experiments. Therefore, the Bragg peaks were spread with a rotating spiral ridge filter of brass. The ^{4}He, ^{12}C and ^{20}Ne Bragg peaks were spread to 10 cm and the ^{40}Ar peak to a 4 cm configuration. The depth-dose distributions in water are shown in Figure 4. The arrows indicate the part of the spread

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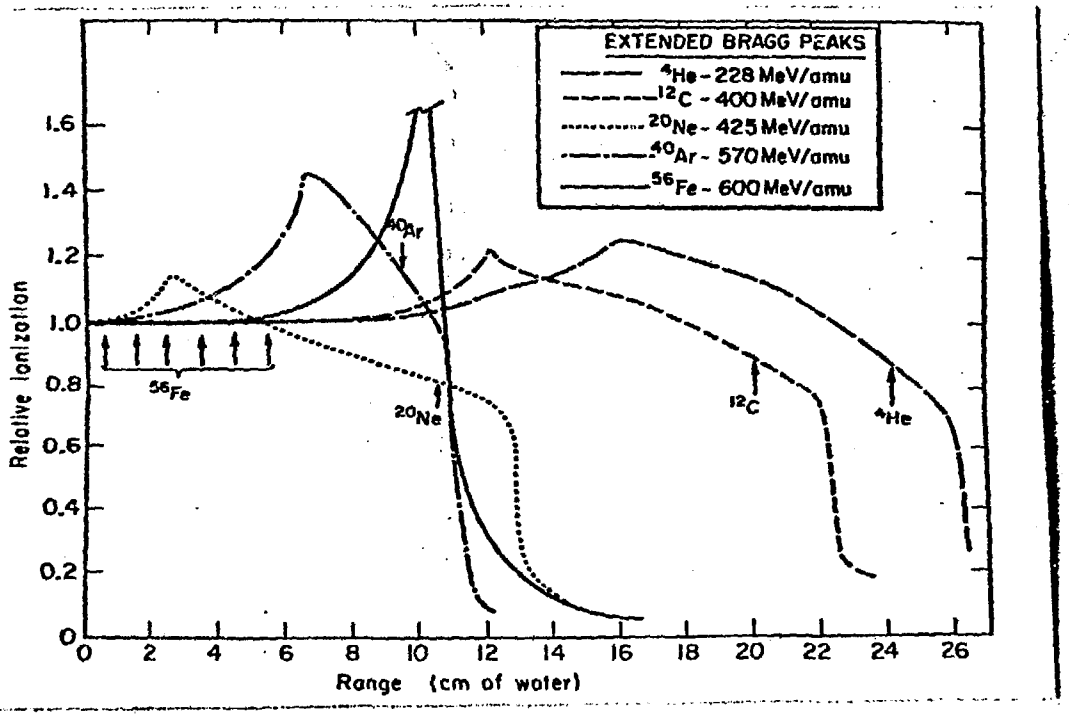
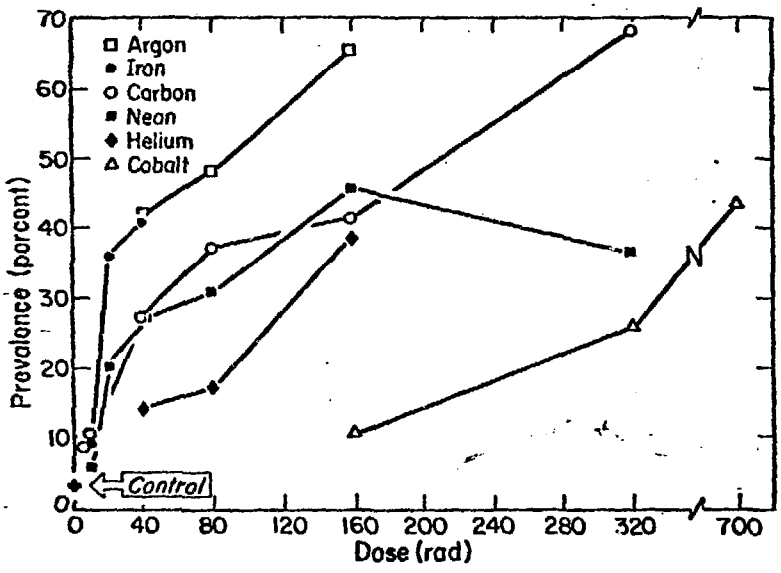


Fig. 4 Depth-dose distributions for the ion beams used in this study. The irradiation positions in the spread Bragg peaks are indicated by the arrows for all the ions except ^{56}Fe. In the case of ^{56}Fe the arrows indicate the plateau region of the beam which was the part of the beam that was used. The estimates of the dose-average LET values were ^{4}He: 1-2 keV/μm, ^{12}C: 80 keV/μm, ^{20}Ne: 150 keV/μm, ^{56}Fe: 180 keV/μm, and ^{40}Ar: 650 keV/μm.

Bragg peak that were used in the exposures. The irradiation position in the Bragg peak was controlled by interposing a variable water column absorber equivalent to the depth positions indicated by the arrows in Figure 4. By using different positions on the Bragg peak a range of LET values can be obtained. The dose-average LET values ranged from about 0.3 keV for ^{60}Co gamma rays to about 650 keV for ^{40}Ar. Mice were positioned in the heavy ion beams to allow exposure of the head and thorax. The ovary was not irradiated.

We chose to use prevalence of tumors as the endpoint and animals were killed at about 600 days of age. The advantage of this procedure was that it was more economical than a duration-of-life study and deaths from competing causes were almost eliminated. We believe that the prevalence data obtained in this way is comparable to that previously found by us in duration-of-life experiments involving either ^{60}Co gamma ray or fission neutron irradiation. Since the promotion by prolactin advances the time of appearance of tumors and all glands were serially sectioned the differences in lifetime incidences and prevalence rate at 600 days are probably trivial.

In the current experiments with heavy ions the aim was to get sufficient comparative data for a broad range of LETs to examine the relationship of RBE to LET. The data obtained so far are shown in Figure 5. It can be seen that there is a general trend of



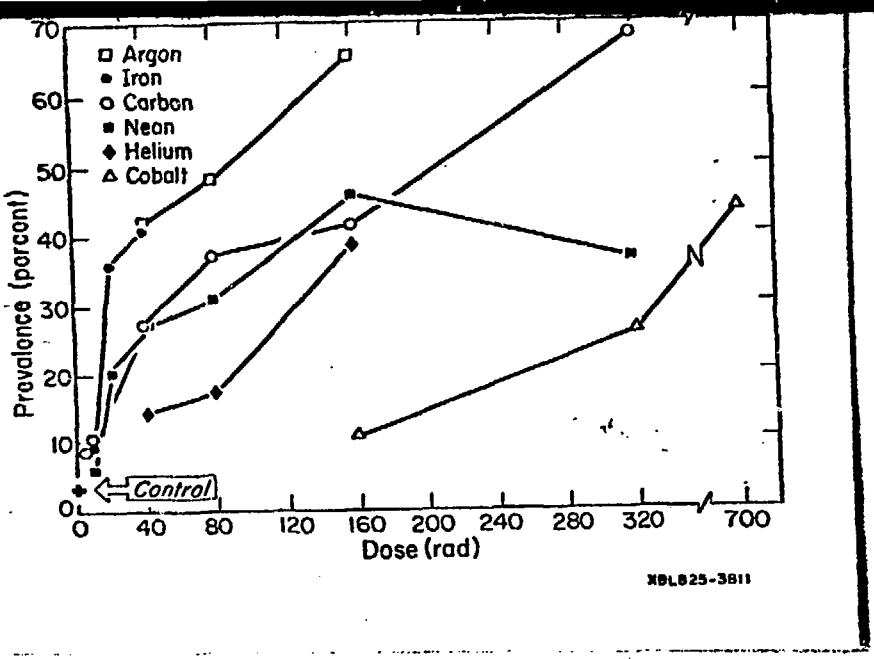


Fig. 5 Prevalence of Harderian gland tumors as a function of dose for the heavy ions indicated. The estimated LET values are given in the legend for Figure 3.

an increase in the initial slopes of the curves with increasing LET. The curves for carbon, neon, argon and iron all show the bending over at relatively low doses that was noted for fission neutron irradiation. Since the dose-averaged LET for the argon beam is well above 100 keV/μm (about 650 keV/μm) the finding of very steep initial slope for the tumor prevalence as a function of ^{40}Ar dose is perhaps at variance with predictions. If the RBE for carcinogenesis in relation to LET behaved similarly to mutation and cell killing we would expect some decrease in RBE at very high LET values. The data is not yet sufficiently precise to delineate the RBE-LET relationship but it is possible that the RBE value may plateau rather than peak at LET values of 100 keV/μm or greater. The marked effectiveness of the ^{56}Fe beam in producing tumors is of interest. We have noted that irradiation with this beam produces multiple tumors in the individual Harderian glands and in both glands with a higher frequency then with any other of the beams. The interactions of ^{56}Fe ions with tissue elements are complex and the LET value for such a beam may be misleading. However, it is clear that further investigations of the carcinogenic effects of this heavy ion would be productive.

The spread Bragg peaks are not homogeneous beams and are less suitable than the plateau region of the beam for biological experiments. It may now be possible to obtain the appropriate range of LETs with the plateau regions of the beams for future experiments. It has been noted that for cell killing in mouse tissues the variation in radiation response between heavy ions cannot be accounted for on the basis of differences in LET

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alone and that the particle mass is of importance [36]. The influence of mass on the carcinogenic effect of heavy ions will also have to be investigated.

SUMMARY

Despite the increasing amount of data and understanding of the factors that influence the shape of the dose-response curve for induction of cancer with high-LET radiations we have no satisfactory model for the responses. It is clear that neutron effects are not simply additive since fractionation increases the effect of neutron irradiation. Preliminary results from experiments with heavy ions suggest that the RBE to LET relationship for cancer induction does not show a marked peak at 100 keV/μm as has been seen for some other endpoints. The results demonstrate that irradiation with heavy ions of iron is highly carcinogenic.

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