after drug administration is much too low to be compatible with the observed delay in tumour growth. If, however, assay of surviving fraction is delayed until 48 hours, then the value obtained for surviving fraction may be up to 50–100 times higher than that measured at 2 hours (depending on the drug dose and tumour size) and perfectly compatible with the delay in tumour growth. Data on cell loss from treated tumours and the proliferation rate of surviving clonogenic cells indicate that ' recovery from potentially lethal damage ' is the main factor operating to produce these results. The increase in measured surviving fraction between 2 and 48 hours appears to be considerably less with MeCCNU than with cyclophosphamide or BCNU, and this is probably the reason why MeCCNU is by far the most effective of these three agents in terms of growth delay and tumour cure for the EMT6 tumour. Very low surviving fractions measured at short times after administration of bleomycin appear to be artefactual, owing to drug carry-over and high drug sensitivity during the making of cell suspensions.

Fractionated irradiations of a rat tumour and foot at different dose-rates

1605A

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Experiments were performed to investigate the effectiveness of X-rays applied at dose-rates of 4 Gy h^{-1} and 204 Gy h^{-1} for the induction of tumour growth delay and normal tissue damage. The aim was to determine whether the therapeutic ratio for doses applied at a dose-rate of 4 Gy h^{-1} is equivalent to that obtained at a dose-rate of 1 Gy h^{-1} presently used in some clinical trials, in order to shorten the irradiation time for the patient.

A rat rhabdomyosarcoma was used to evaluate the effectiveness of four daily doses of 300 kV X-rays administered at a dose-rate of 4 Gy h^{-1} as compared with four daily doses at a dose-rate of 204 Gy h^{-1}. Skin of the rat foot was used as a normal tissue. Four daily doses at dose-rates of 4 and 204 Gy h^{-1} were given; these were followed 1 or 3 days later with an acute dose of 15 Gy. The results indicate that the treatment of the tumour at 4 Gy h^{-1} is less effective per unit dose than the treatment at 204 Gy h^{-1}. The greater amount of sublethal damage repaired during the low-dose-rate irradiation may account for the relative decrease in effectiveness of the treatment at 4 Gy h^{-1}.

However, fractionated irradiation of the rat foot at 4 Gy h^{-1} seems to be more effective per unit dose than fractionated irradiation at 204 Gy h^{-1}. Experiments are in progress to determine whether the use of the anaesthetic Ethrane in the low-dose-rate treatments, in contrast to the Nembutal used in the acute irradiation treatments, might be responsible for the differences observed.

Model studies with hypoxic sensitizers

1606A

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Many model tumour studies have indicated that the application of hypoxic sensitizers is not effective when combined with tumour irradiation in conventional small fractions. It appears, as in the case of hyperbaric oxygen treatment, that this is due to re-oxygenation of the tumour. For this reason, studies were performed with Ro-07-0582 in combination with small dose fractions of radiation on a poorly re-oxygenating tumour—mouse osteosarcoma C22LR. In initial studies it seemed not to respond to application of the sensitizer, but it appeared that this was due to the fact that re-growth delay was used as the treatment end-point and that, owing to a rapid repopulation rate, re-growth was not dependent on the hypoxic cells. When this was modified by pretreatment of the tumour with a large single dose of radiation, the subsequent application of small fractions of radiation were significantly affected by the hypoxic sensitizers. Since toxicity data for the nitroimidazole compounds seem to limit their application to a small number of doses, we then investigated whether,