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CENTER FOR HUMAN RADIOBIOLOGY

Fact Sheet on

Theory of the Induction of Bone Cancer by Alpha Radiation

A three-stage model of the induction of osteosarcoma by alpha particles fits all the data for radium in man and in the Salt Lake dogs over the entire dose-time-response surface. The theory is based upon what is known and what is likely to be verified regarding the mechanisms affecting endosteal cells. (The abstract of a paper submitted to Radiation Research is on the reverse side.)

We will try to fit all existing osteosarcoma data for alpha radiation in man, dog, and mouse. If the theory continues to fit as well as we believe it will, and if a number of the many predictions from the theory are verified, then it could be used to predict the risk to man of the induction of bone cancer by alpha radiation for any combination of doses and dose rates at any level from any alpha emitter such as thorium, uranium, plutonium, or the other transuranic elements.

This new approach to the problem of the toxicity of internal emitters is, we believe, a breakthrough, because it shows that synthesis of the animal and human data within a logical, mechanistic framework is possible.

We are now working to extend the theory to the molecular level in order to bring in the effect of LET. If successful, we should have a new theory of cell killing and a new subcellular theory of the induction of bone cancer. One of the early results of these new theories is that it is difficult to keep a two-initiation model from going linear at all doses below the plateau unless the target cells lie flattened against the bone surface. The probability of hitting two targets within the cell nucleus with one alpha particle predominates over the two-hit-two-particle mode at all endosteal doses less than about 150 rads in a spherically shaped nucleus. This transition dose, which we call eta (η), is over twice as high as that predicted by the Kellerer-Rossi model because the latter ignores the probability of killing a cell by the same alpha particle that yields an initiation. On the other hand, a cell flattened against bone surface—where we think the target cells actually lie—will probably give an eta value of some 50 rads for bone surface sources and perhaps 20 rads for bone volume sources. Surface sources like Ra-224 and Pu-239 should therefore give dose response curves which are somewhat more linear than the volume seekers, Ra-226 and Ra-228, in the observable range of doses below the plateau. At still lower doses, all alpha response curves are probably linear.

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J. H. Marshall and P. G. Groer. THEORY OF THE INDUCTION OF BONE CANCER BY ALPHA RADIATION. Submitted to Radiation Research.

A theory of the induction of osteosarcoma by alpha particles fits data for radium in man and dog over the entire dose-time-response surface. The theory postulates that an endosteal cell near bone surface is transformed by three events. Two initiation events, each with a probability of $4 \times 10^{-8}/\text{rad}$ are produced in a single cell by two alpha particles. A promotion event then occurs at a rate of $10^{-2}/\text{yr}$, not related to radiation, but proportional to the rate of bone remodeling. In competition with these events is the killing of any endosteal cell by an alpha particle with a probability of $10^{-2}/\text{rad}$. Killed endosteal cells are assumed to be replaced by stem cells at a rate of $10^{-1}/\text{day}$. Postulated tumor growth takes 3-6 yr. These values for man are preliminary. The probability per rad per cell of each initiation appears to be ~ 10 times larger in dog than in man.

A new method of three-dimensional analysis provides a compact way to report more fully the data for internal emitters and eliminates competing risks from comparisons between theory and experiment. The theory provides an explanation for latent period, for the protraction effect for ^{224}Ra in man, for the narrow time-distribution of tumors in dog, for the wide time-distribution of tumors in man, for the plateau in cumulative incidence at 17-31% observed so far for ^{226}Ra - ^{228}Ra in man, for the much higher plateau in dog (92%), and for the steep decrease of tumor rate with decreasing dose below the plateau. Tumor rate P is shown to be a function of endosteal dose D , and at less than 1 rad/day to be independent of endosteal dose rate F . At low doses, P is proportional to D^2 . At high doses, P plateaus and becomes independent of D . The onset of the plateau is governed by the mean lethal dose to endosteal cells.

The theory provides a number of firm predictions. (1) The mean time of tumor appearance will stop increasing with decreasing intake of radioactivity at about $2/3$ the life span. (2) Growth hormone will produce a calculable increase in tumor rate in dogs injected with ^{224}Ra . (3) In the human ^{224}Ra cases, tumor rate will be found to decrease exponentially with a rate of roughly 1%/year. (4) A nuclide of intermediate half-life like ^{228}Ra will be found to induce more tumors than ^{226}Ra for the same endosteal dose. (5) At high dose rates the induction of tumors will be suppressed by about the factor $(1 + 0.1F)^{-1}$, where F is in rads/day. (6) Only 7% of the living ^{226}Ra - ^{228}Ra cases with skeletal doses over 1000 rads will develop osteosarcomas, because their normal life expectancy averages about 12 years and their expected tumor rates average 0.6%/year. That tumor rate at lower doses in man is better represented by D^2 than by D will be tested further in a later paper.

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