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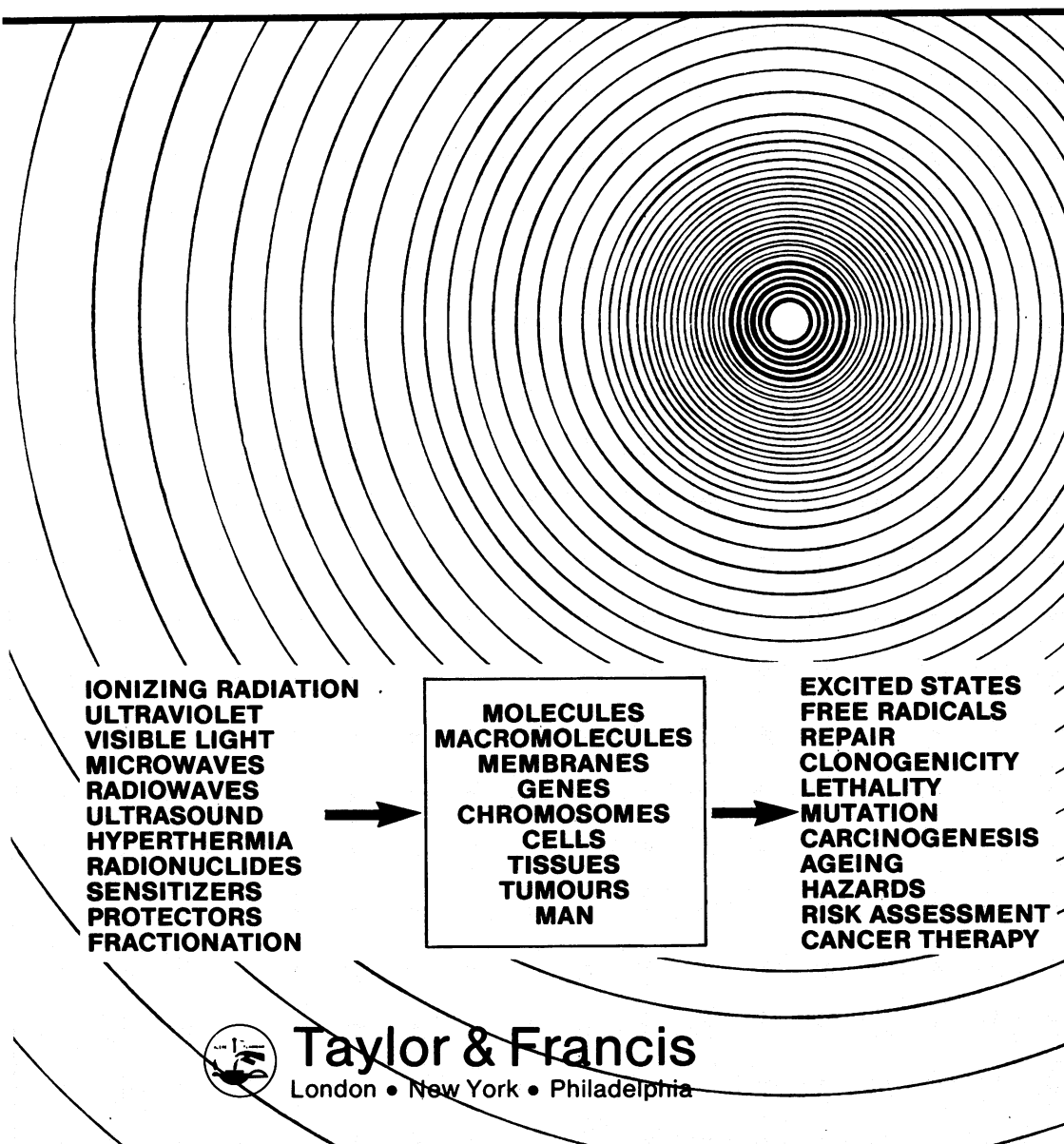

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Dose and dose-rate dependence for bone sarcomas in radium-224 patients

A. M. KELLERER, H. SPIESS and D. CHMELEVSKY

Institut für Med. Strahlenkunde der Universität Würzburg,
Versbacher Straße 5, D-8700 Würzburg, FRG

Risk estimates for ionizing radiations are largely based on epidemiological findings on persons exposed to relatively high doses of one or several gray. Extrapolations to the small doses relevant for radiation protection are, therefore, unavoidable, and such extrapolations require a variety of assumptions and models. The most widely used model is the linear-quadratic dose dependence. The common assumption is that the linear component is predominant at low doses and independent of dose rate, while the quadratic component decreases as the dose rate is reduced. Accordingly one uses observed cumulative incidences of tumours at high doses and multiplies these with assumed dose-rate reduction factors (DREF) before one applies a linear extrapolation to small doses. While there are differences in the assumed values of the DREF, the basic rationale is accepted, and it is in line with a variety of observations for sparsely ionizing radiations.

The situation is more complex for densely ionizing radiations. Epidemiological data are available for incorporated α-emitters, but most of the studies, e.g. in uranium miners, thorotrast patients or dial painters, permit only rough statements on the dose–effect relation and no conclusions concerning a dose-rate dependence. Experimental investigations with animals and cell studies, on the other hand, have recently provided evidence of a reversed time factor, i.e. of an increased effectiveness of a specified absorbed dose when it is fractionated or protracted over hours or over longer durations. Such observations are of evident importance for risk estimates of small doses of densely ionizing radiations, and for the current discussion of a revision of the quality factor in radiation protection. We have therefore reanalysed the one set of epidemiological data, the observations on bone sarcomas produced in the German radium-224 patients, that can provide direct information on the dose-rate dependence for effects of densely ionizing radiations in man.

Shortly after World War II more than 800 patients were injected in a German clinic with large activities of radium-224, an α-emitter with 3·5 days half-life, for the intended treatment of bone tuberculosis and ankylosing spondylitis. Subsequently more than 50 bone sarcomas have occurred among this collective of patients (Mays and Spiess 1984, Mays *et al.* 1986, Chmelevsky *et al.* 1986, 1988). Spiess and Mays (1973) concluded in an earlier analysis that, at equal mean absorbed doses in the skeleton, patients with longer exposure times had a higher incidence of bone sarcomas. The earlier analysis was based on approximations, and it did not account for the varying times at risk of the individual patients. A re-evaluation of the continued follow-up was therefore performed with more rigorous statistical methods.

In the first part of the study the existence of the reversed dose-rate effect is established in terms of a suitably constructed rank-order test. It is seen that at equal mean skeletal doses the bone sarcomas tend to occur more frequently in the patients who had received the injections over longer protraction periods of up to several years. The analysis shows that this conclusion is not due to the influence of the confounding factor age at treatment. In a second part of the analysis it is then inferred that the results are consistent with a linear no-threshold dose dependence under the condition of constant exposure time, while there is a steeper than linear dependence on dose when the exposure times increase proportionally to dose. A maximum-likelihood fit of the data is performed that indicates proportionality of the tumour expectation, R, to mean skeletal dose, D (in gray), with an added factor that contains the treatment time, τ (in months):

$$R = 0{\cdot}0055 \times D \times (1 + 0{\cdot}18\tau)$$

An interesting implication of this relationship is that the reversed time factor appears to apply at small doses as well as at high doses. However, it must be noted that the observations pertain only to mean skeletal doses of 1 Gy or more, and that the doses to the endosteal cells are about eight times higher. At such doses cells are traversed by several α-particles, and the reversed time factor can therefore be explained by the fact that the yield of transformed cells increases less than linearly with the number of α-particles per cell.

A current epidemiological follow-up of patients subjected to present-day low-dose radium-224 therapy of ankylosing spondylitis is still incomplete, but it will ultimately add to the present experience.

Commentary on discussion

Osteosarcoma induction in ^{224}Ra therapy patients is an important data resource for high-LET (α-particle)-induced cancer in man. A substantial number of osteosarcomas have arisen in these patients and the data analysis presented by Kellerer represents a significant advance in our understanding of dose effect, particularly with regard to the distribution of mean skeletal dose and the effects of dose-protraction. These new analyses provide a more convincing demonstration of an enhanced yield of osteosarcoma with dose protraction than that originally provided by Spiess and Mays (1973). The mechanistic aspects of this and its relevance to human radiological risk remain, however, uncertain. Discussion centred on these problems and, in particular, on the relatively high α doses ($\sim$8 Gy) calculated for cells at the endosteal bone surfaces. At this mean dose it was suggested that the fluence of α-particles per endosteal cell could allow for a 'reverse

time' factor to operate such that single target cell transformation was favoured when α-particle traversals were spread over time. The validity of this, particularly at such high total absorbed doses depends to a large extent on the intrinsic α-particle sensitivity of the osteogenic target cells to inactivation and possible differences in their patterns of proliferative response following acute and protracted α-irradiation. A conventional radiobiological view would make 8 Gy of α-particles a supralethal dose to a single cell. Since, however, bone has a complex structure and the distribution of osteogenic target cells and ^{224}Ra is likely to be inhomogeneous, 'mean skeletal dose' may be a rather misleading parameter. Osteosarcomagenesis following such high α doses to bone could be explained if target cels were, in fact, located in marrow close to bone surface. Given these uncertainties we should perhaps exercise caution when evaluating the reverse time factor for ^{224}Ra human osteosarcomagenesis and its relevance to the low-dose problems of radiological protection.