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h.b. kal, a.j. van der kogel
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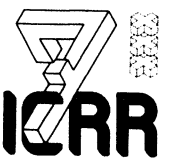

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CONTENTS

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SOMATIC AND GENETIC EFFECTS

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DOSIMETRY, RADIONUCLIDES AND TECHNOLOGY

MODELS OF CELLULAR RADIATION ACTION

A.M.Kellerer
Institut für Medizinische Strahlenkunde der Universität Würzburg, Versbacher Str.5, D-8700 Würzburg, Germany

I. *Introductory Remarks*

Models, as the ethymology of the word says, are *measures* of our knowledge of the mechanisms underlying observed phenomena. In radiobiology they are more often testimony to our lack of knowledge of fundamental mechanisms; in this sense the present development is one away from models towards actual detailed knowledge. But models - faulty as they may be - are still required as guideposts towards new experiments and as conceptual framework that facilitates discussion. They will be useful only if they are not taken too literally, and at the present state of knowledge, no radiobiologist ought to aim at precise and complete agreement between his equations and the experimental data. What one can hope for, is merely the identification of recurrent trends and of essential characteristics of the dose-effect relations in their dependence on parameters, such as radiation quality, dose rate, or oxygen tension.

The subsequent remarks will, accordingly, deal with problems and propositions rather than equations and numerical data. Relevant as a look back to the role of target theory and the more questionable role of multi-target or multi-hit theory could be, it will be omitted. Neither can a full synopsis of models of cellular radiation action be attempted within the constraints of the allotted space.

II. *The Linear-Quadratic Dose Dependence*

There are simple and fundamental conclusions that follow from microdosimetry - the term *microdosimetry* being used in its general sense as the physics of the microscopic distribution of energy imparted by ionizing radiations. One of the most general conclusions is that *at low doses any dose-effect relation for autonomous cells must be linear*. A *low dose* in the microdosimetric sense is one where a charged particle appears in only a minor fraction of all cells, or cell nuclei. The number of such cells is then evidently proportional to absorbed dose. For sparsely ionizing radiations low doses are fractions of one mGy, for densily ionizing radiations low doses are fractions of one Gy. The term *autonomous* was introduced by H.H.Rossi (20) to refer to the condition that the fate of the exposed cell is unaffected by radiation effects on its neighbours or on the tissue as a whole.

+) *Support by Euratom (Contract BIO-286-81D(B)) is acknowledged.*

For *genetic* effects the existence of a linear component at low doses follows, therefore, from first principles of microdosimetry. Dose relations for chromosome aberrations must have a linear component; estimates of hereditary risks of ionizing radiations can equally utilize the postulate of a linear relation at low doses (23,32). The situation for *radiation carcinogenesis* is more complicated; linearity can not be postulated even for very low doses, as inter-cellular processes and tissue factors can play, and have been shown to play (36,28,29), an important role.

At intermediate and higher doses the dose dependence for cellular effects is more complex and a variety of equations has been employed. However, the *linear-quadratic dependence* on absorbed dose has taken a predominant role in recent years and, at least for cell inactivation and chromosome aberrations, it is usually adequate. It has occasionally been said that the linear-quadratic dependence is trivial because any observed function can, in its initial part, be approximated by a linear term, a linear-quadratic term, or if more precision is required, by a combination of higher powers of absorbed dose. This truism may be misleading if it conceals the fact that the linear-quadratic relation covers the observed data of many experiments with mammalian cells over an appreciable range of absorbed doses, and that it is therefore more than a mathematical triviality. Subsequent considerations on the RBE-dose relation will confirm the point.

It is well known that there are at higher doses deviations from the linear-quadratic dependence. This would require a separate consideration, but in the context of the present discussion it may merely be noted that the tail of the dose relation is frequently influenced by technicalities of the experiment and is less indicative of basic mechanisms. This aspect is therefore omitted from the present survey of essentials.

On the basis of some observed dose-effect relations a case can be made for the linear-quadratic relation; others are far more complicated. But the evidence has gained additional weight by the study of RBE-dose relations. Rossi (26) has emphasized the point that such studies remove complexities of the dose-effect relations which are independent of radiation quality, and that they have, accordingly, greater significance than the mere study of the dose-effect relations. RBE-dose studies have, indeed, led to the recognition of large neutron RBEs at low doses; they have also demonstrated a dependence of neutron RBE on dose that provides strong evidence for linearity of cellular damage with neutrons, and for quadratic relations with γ- or x-rays. From the studies of tumor induction or life shortening it appears that any linear components for x-rays must be much less than those observed for cellular inactiviation. In conclusion: *RBE-dose relations, rather than dose-effect relations, are the essential argument for the linear-quadratic dependence of cellular damage on radiation dose.*

Pragmatic implications of the linear-quadratic models are evident and require only brief reference. The very concepts and quantities of radiation protection are linked to linearity, although this is not always sufficiently appreciated. The established notions may by now be so familiar that one tends to overlook the fundamental difference of philosophy between radiation risk assessment with its linear postulates and toxicology with the more common assumption of a threshold.

Radiation protection is, of course, not the only area where assumed or inferred dose-effect relations for cellular effects have pragmatic implications. Radiation therapy is another area with its own empirical or seri-

empirical models. The linear-quadratic model is, nevertheless, relevant. This may appear surprising in view of the Ellis formula that accounts for the influence of protraction and fractionation. One can show, although this is not widely known, that this formula corresponds to the assumption of a power function for the survival curve (with Ellis' original coefficients: $ln\ S \sim D^{1.32}$). Nobody expects a cellular dose-effect relation to follow such a relation that has zero slope at the origin. This would seem to invalidate the Ellis-formula, and, indeed, more realistic treatments in terms of the linear-quadratic relation have been proposed by Fowler and Stern (9) and by Barendsen (2). Of course, this does not invalidate the Ellis-formula and its important role as a clinical guideline, within the limited range of conventional fractionation schemes. One can replace the broken power of dose by a closely coincident linear-quadratic term (16) and obtains then a formula that is nearly unchanged in the range of validity of the Ellis-equation, but gives meaningful values even at lower doses and dose rates and could therefore be useful also in intracavitary therapy. The example testifies to the fact that there is not only theoretical interest in models of cellular radiation action, but a continuing practical need as well.

III. *The Evolution of Relevant Studies*

The fundamental idea is simple and has been recognized since the work of Lea and Sax on chromosome aberrations (21). A *second order process* or *dual action*, as it has been termed in a later approach (19), would lead to a quadratic dependence on absorbed dose if the spatial distribution of energy imparted were uniform. In reality an added linear component appears because energy is imparted to the cell in correlated clusters on the tracks of charged particles; even at smallest doses the local concentrations of energy can be large, and they depend then only on radiation quality not on dose.

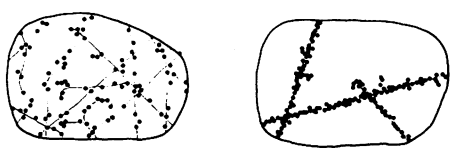


Fig. 1 Schematic diagram of the distribution of energy transfers (dots) in a cell nucleus exposed to sparsely ionizing and densily ionizing radiation.

The schematic diagram of Fig.1 can help to indicate the concepts and facilitate the terminology. It represents schematically the situation of a sparsely ionizing and a densely ionizing radiation. The dots stand for *energy transfers*, and from these energy transfers sublesions may be produced. One might conceive of the sublesions as single strand DNA breaks (SSB) and of the lesions as double strand breaks (DSB); but sublesions could also be chromosome instabilities and lesions could then be observable chromosome aberrations. Even the schematic two-dimensional diagram indicates the potential complexity of interactions in a random pattern of energy transfers and resulting sublesions that may interact pairwise. Evidently there is no lack of possible models and free parameters. Whatever

postulates will be invoked, it is plausible to assume an interaction probability between sublesions that decreases with distance of initial separation. Lea assumed a constant interaction probability up to a critical distance, and zero interaction probability beyond this range. Of course, this assumption was introduced not as an actual postulate but merely as a pragmatic approximation.

With this explanation one can take a general view and classify the approach of Lea or similar treatments, as *proximity models*. The term refers to the assumption that sublesions are formed randomly by energy transfers and that pairs of neighbouring sublesions interact with probability that increases with their proximity. From the diagram of Fig.1 one sees intuitively that interaction of *intra-track* sublesions must predominate in the case of densely ionizing radiations, while interactions of *inter-track* sublesions are more frequent in the case of sparsely ionizing radiations. In the actual 3-dimensional case it is even more unlikely that energy transfers from independent particle tracks come into close proximity, while close neighbours will always exist within particle tracks, and especially within the tracks of densely ionizing particles.

The unspecified use of the term *interaction probability* of energy transfers or sublesions has in the past led to confusion. The term does not refer to a *direct* interaction, but is a *probabilistic* notion that refers - certainly for the inter-track effect, but probably also for the intra-track formation of damage - to the outcome of a complex chain of molecular and metabolic events that may lead from the production of free radicals to DNA-damage and then - with shorter or longer spatial and temporal separation - to successful or faulty repair. The relevant damage is never 'directly' produced by the initial processes of energy transfer. Obvious as this point should be from its original use in the context of the formation of chromosome aberrations, it is even now not sufficiently appreciated; inherently similar notions such as *sublesion interaction* or *misrepair due to the formation of neighbouring lesions* are then treated as alternatives rather than different designations of the same process.

When microdosimetry was developed by Rossi and his colleagues a powerful new tool for experimental assessment of radiation quality became available. One can determine actual energy concentrations within microscopic volumes. But one must realize that the familiar microdosimetric measurements answer a question that is not entirely analogous to the problem of the prox-

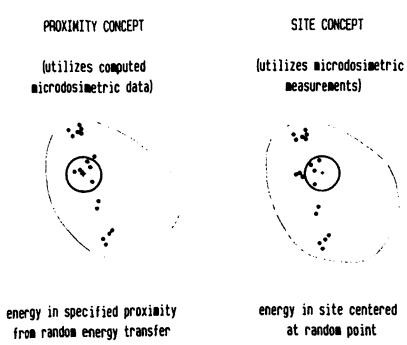


Fig. 2

Schematic diagram to illustrate the relation of the proximity and the site concept. The proximity function is utilized in the proximity model; it is linked by a general mathematical relation to the dose average of microdosimetric quantities (17). The proximity concept permits a treatment in terms of distance dependent interaction probabilities (20).

imity models. They do not determine the number of neighbouring energy transfers around a randomly chosen energy transfer; they specify instead the number of transfers in a randomly positioned site. A model, therefore, that is based on experimental microdosimetric data must be a *site model*. The scheme of Fig.2 juxtaposes the two concepts, that have here been mentioned because they are recurrent notions in a variety of models that are not always phrased in the microdosimetric terminology. However, they are mentioned also to emphasize the fact that both approaches are inherently similar in invoking local *measures of energy concentration* over distances that are relevant to the accumulation or fixation of cellular damage. Site and proximity models are variations of the same theme.

With this convention on terminology one can now trace briefly the development from the work of Lea to current models. As is well known, Lea and Sax have compared the dose relations of chromosome aberrations for neutrons and x-rays. They used the estimated frequencies of intra-track and inter-track neighbours to determine interaction distances of sublesions, i.e. chromosome breaks, and they deduced distances up to 1 μm, i.e. the curved shape of the dose-effect relation for x-rays was evidence for long range interactions.

The approach of Lea and Sax could have offered itself to ready translation into the concepts and quantities of microdosimetry. However, the first application of microdosimetry took different and independent lines. An attempt was made by Rossi and coworkers (30,22) to see whether a critical threshold of specific energy in certain assumed sites would correlate with the experimental data. The lack of agreement with experimental results led to the more generalized approach that ascribes an increasing effect probability to increasing values of specific energy - one may note that there are recent approaches (4) of the same nature. When this assumption was tested against a variety of experimental data, the conclusion was drawn that a quadratic dependence on specific energy agreed with a wide range of experimental data. This led to the microdosimetric analysis of dual radiation action (19). Subsequently the close analogy to Lea's results for chromosome aberrations was appreciated.

From this point of initial agreement the development led to the present state. Neary had extended the studies of Lea. From his work with soft x-rays (24) he inferred interaction distances that tended to be less than those earlier deduced. Goodhead and colleagues (11) extended the investigations of Neary to still lower x-ray energies and, found - as did Virsik and Harder in their chromosome studies (34,35) - further evidence for short range interactions. This is in agreement with earlier conclusions from track segment work (1) and from studies of DNA damage by heavy ions (25). The general conclusion is that the proximity model with constant interaction probability or the analogous site model is inadequate. An independent and simultaneous derivation of this result came from experiments with spatially correlated heavy ions (27,18). Rossi and his colleagues had shown in these experiments, that a majority of the intra-track lesions are formed from short range interactions. Together with the sigmoid shape of the survival curve, and the implied requirement of long range interactions, this led to the conclusion of an interaction probability of sublesions rapidly declining at distances below 50 to 100 nm, but reaching out to distances of the order of a micrometer.

At this point there was remarkable agreement. There was also agreement with earlier results of Chapman et al.(6) who had identified characteris-

tic differences in the effect of modifying factors on the linear intra-track component and the quadratic inter-track component. If the intra-track action pertains to much shorter distances than the inter-track action, the marked differences are understandable.

A similar consideration pertains to the OER. If observed lesions result from a second order process then - as elementary arguments can show - the OER for the intra-track effect should equal the square of the OER for the sublesions. For the inter-track effect the OERs of lesions and sublesions should be the same. There is, however, no experimental evidence that the OER for the linear component of cell survival or other cellular effects is larger than that for the quadratic component. The sublesions involved in the linear process must therefore have a considerably smaller OER than in the inter-track mode. The reduced OER of high LET radiations may, of course, involve additional factors, such as saturation effects.

IV. *Interpretations*

The quadratic model has been rejected by Goodhead (12,13) in favor of a proposed interpretation that he has labeled TERS. In the acronym TE stands for *threshold energy* and for the assumption that a critical energy of 100 to 300 eV causes, in sites of 3 nm diameter, repairable lesions, while more than 300 eV (for mutations twice the amount) cause non-repairable lesions, the predominant mode for densely ionizing radiation.

One may be reluctant to adopt the notion of defined 3 nm sites with two energy thresholds for two types of lesions; but the postulate appears flexible enough to be replaced by a probabilistic dependence. A more serious limitation could be, that site sizes (or effective sizes) and thresholds (or effective thresholds) for two types of presently undefined DNA-damage confer to the model too many parameters to allow verification or falsification. The problem is common with other models, too, but it is here particularly evident since the parameters determine merely the linear component. An independent feature is invoked to account for the curvature of the dose dependence.

The additional feature is RS, *repair saturation*, the assumption that among the extensive repair of radiation induced damage it 'seems likely that at least one of these repair steps becomes less efficient with increasing radiation dose, probably due to saturation of the repair system'.

A dose dependent loss of compensation or repair efficiency had been invoked before most of our present knowledge on enzymatic repair mechanisms was available (14,15). However, for the presently known mechanisms of *short patch*, *long patch*, *recombination*, and *SOS repair* - even if they were all operative in eukaryotes - it is difficult to conceive of saturation at doses of a few gray. It is, in fact, difficult to analyse these mechanisms except at far higher doses. Experiments by Virsik and Harder (33) on chromosome aberrations indicate that the half times of repair are independent of dose. Recent work by Blöcher and Pohlit (3) gives the analogous results for DSB repair in mammalian cells. The work of Wheeler and Wierowski on DNA-repair in the irradiated rat brain (37) could be cited in support of saturation of a slow repair component. However, the data show unchanged repair times in the relevant dose range below 12 Gy, and any slow-down observed at higher doses may well be a tissue effect. There is, therefore, at present no experimental evidence and no feature of the known repair processes that supports the idea of repair saturation or repair overload.

The dual action model, or any sublesion interaction models of similar nature, are simpler in the sense that they invoke merely one mechanism. But it is evident that the general formulation in terms of distance dependent interaction of sublesions contains also, in effect, many degrees of freedom. Present data are as yet insufficient for the identification of actual mechanisms. Certain firm conclusions are nevertheless reached, as can be illustrated by a further elementary but general application of microdosimetric data, in particular, of the *proximity functions* (17).

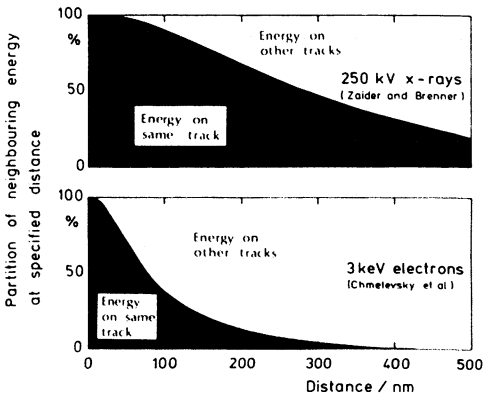


Fig. 3

The average partition (at a dose of 1 Gy) of energy imparted around an energy transfer into contributions on the same particle track (linear term in dose) and on other tracks (non-linear term in absorbed dose).

The data are based on computed proximity functions (5,7).

Fig.3 shows that the intra-track neighbours dominate by far at small distances. As follows readily, any curved dose dependence must reflect interaction of sublesions or accumulation of radiation effects over distances beyond the extension of the dark areas. This requirement is general, and entirely independent of the processes that may be invoked. DNA double-strand breaks would therefore appear not to be the critical lesions, as indicated in the diagram of Fig.4.

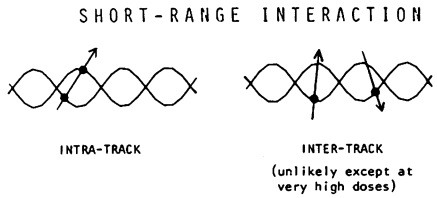
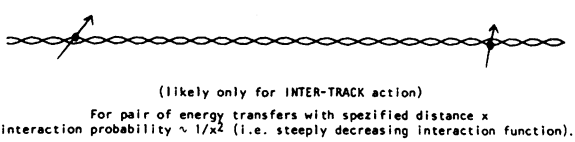


Fig. 4

Short-distance interaction of lesions by separate particles is unlikely at doses of biological interest.

There are, on the other hand, notable results on a quadratic, or linear-quadratic, dose-dependence for non-repaired DSBs, not only in the data by Frankenberg (10) for yeast but also in the results of Blöcher and Pohlit (3) for Ehrlich-Ascites cells. Such unrepaired lesions might be related to cell death, and they may also be involved in other cellular radiation effects. However, this would require the identification of the mechanism that can accumulate damage over distances of fractions of a micrometer. Could energy conduction in the DNA-molecule be responsible for such interactions? Or could the lesions be caused by the failure of recombination or SOS-repair, i.e. forms of repair where patches of thousands of nucleotides (i.e. DNA threads > 0.5 μm, if extended) are replaced, and where the presence of a second DNA lesion within the replacement segment could cause the failure of repair?

Fig. 5 The schematic diagram stands for interaction of damage over very long DNA patches (>1000 nucleotides). This type of misrepair could be envisaged if recombination- or SCS-repair is operative in eukaryotes. The inter-track effect predominates, because the mean number of neighbouring energy transfers on other tracks at distance x is proportional to x^2.



Whether error prone and dual lesion sensitive super-long patch repair is relevant to the action of ionizing radiations on eukaryotic cells is, at this point, mere speculation. But it is an intriguing supposition, in view of an observed quadratic dose dependence for unrepaired DSBs. It is furthermore attractive to note that a linear array of potential targets that can pairwise interact will lead to a distance dependence of lesion formation that is proportional to $1/x^2$ or is even steeper (see the diagram of Fig.5); such dependences have, in fact, been deduced from the correlated ion experiments (18) and from the reanalysis by Brenner and Zaider of the ultra soft x-ray experiments (5).

V. *Conclusion*

Dual radiation action or, more generally, a second order process in the action of radiation on the cell, appears to be the simplest model consistent with experimental data. But the underlying processes are largely unresolved, and other or additional mechanisms can not be excluded. Further progress in the analysis of repair processes, and mechanisms of energy transfer in and around the DNA will be required; microdosimetric studies both on the nanometer and the micrometer level will be equally important.

Curtis has recently brought together essentials of current models (8). The resulting unified treatment covers a broad range of sublesion-interaction or misrepair models. As many of these models, it disregards or simplifies one microdosimetric aspect; it invokes a uniform, non-stochastic, i.e. dose dependent, increase of interaction frequency or misrepair probability. On microdosimetric principles one should expect a dependence of these processes on local energy concentration. The individual cell can not discern the value of the absorbed dose or the average yield of lesions; it can respond only to the energy imparted to itself, and this may deviate greatly, in a non-Poissonian distribution, from the statistical average. There may, accordingly, be room for a further interlinkage of models.

As members of our species we are the product of faulty DNA-repair; as scientists we owe our profession to the evolution of imperfect theories and error-prone ideas. The need for trial and error can serve as an excuse even for a discussion of models that expose more limitations of knowledge than actual mechanisms of cellular radiation action.

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