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HIGH-ENERGY ELECTRON THERAPY AND THE TWO-COMPONENT THEORY OF RADIATION

by

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In recent years, investigations on irradiated cell cultures have cast new light on radiobiologic effects and also aroused widespread hopes that with these findings radiotherapy could be better understood and problems solved, resulting in better methods for the treatment of tumors.

To-day we know that most of the investigated normal and cancerous mammalian cell cultures show approximately the same radiosensitivity (ELKIND 1960). We know also that roentgen-irradiated surviving cells in a culture will recover completely ('Elkind-recovery', ELKIND et coll. 1964) in a relatively short time after the irradiation (about 10 hours or less). We have further established survival curves (dose-effect relations) for various kinds of radiation and also studied the influence of the surroundings (oxygen pressure, injection of cysteamine etc) on the radiosensitivity of the cells in vitro (BARENDSEN 1964).

On the occasion of a Symposium on 'Fractionation and Dose Rate' Westminster, London, in 1962, many attempts were reported trying to link the medical experiences in radiation therapy with the radiobiologic results, and several new treatment schemes were suggested. Similar ideas have in the

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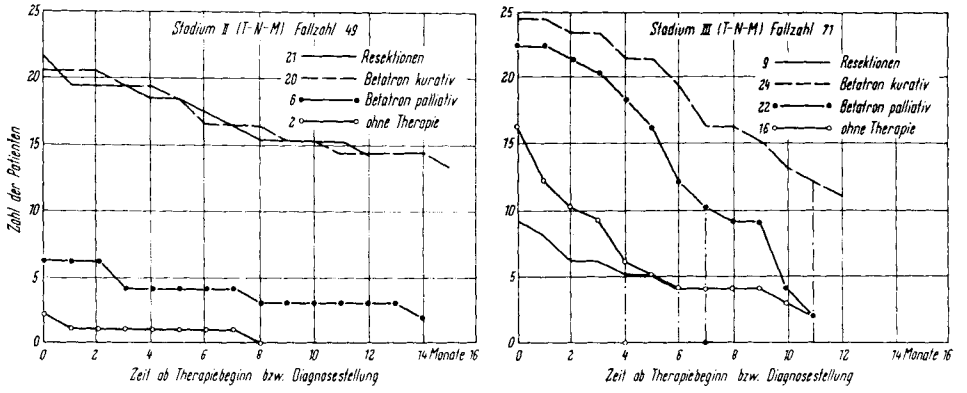

Fig. 1. Survival index for 120 patients with effectively proved bronchial carcinoma, stages II and III, depending on therapy (SCHUMACHER 1964).

meantime been discussed also by other investigators (e.g. ANDREWS 1965, HUG 1964). (It is impossible here to describe in detail all attempts but the reader may get a good impression of the situation by studying the cited literature, especially Brit. J. Radiol. 36 (1962) pp 153—196.)

To-day, developments in radiation therapy are progressing rapidly. The use of megavolt roentgen rays and especially deep therapy with high-energy electrons has increased our understanding and improved results. However, not all the experiences can be physically explained by the better dose distribution and the reduced integral doses (GAUWERKY 1964).

In the present paper, a case treated with high-energy electrons will be described and it will be shown that results from cell cultures are not directly applicable to such conditions (WIDERÖE 1965). The reason is discussed and a new quantitative theory for radiation effects in vivo is advanced.

Treatment example from radiation therapy

We will discuss the treatment of bronchial carcinoma using 35 MeV electrons. Early bronchial carcinoma has already been treated with high-energy electrons but the results were mostly discouraging and not much better than those obtained by conventional radiation therapy (ZUPPINGER et coll. 1964). Only UHLMANN & OVADIA (1961) and HELLRIEGEL (1959) have reported somewhat better results with lesions of early stages. Recently, however, SCHUMACHER (1964) has demonstrated that higher single doses, given at greater intervals (for instance: up to 1 200 rad tumor doses given once a week) give much better

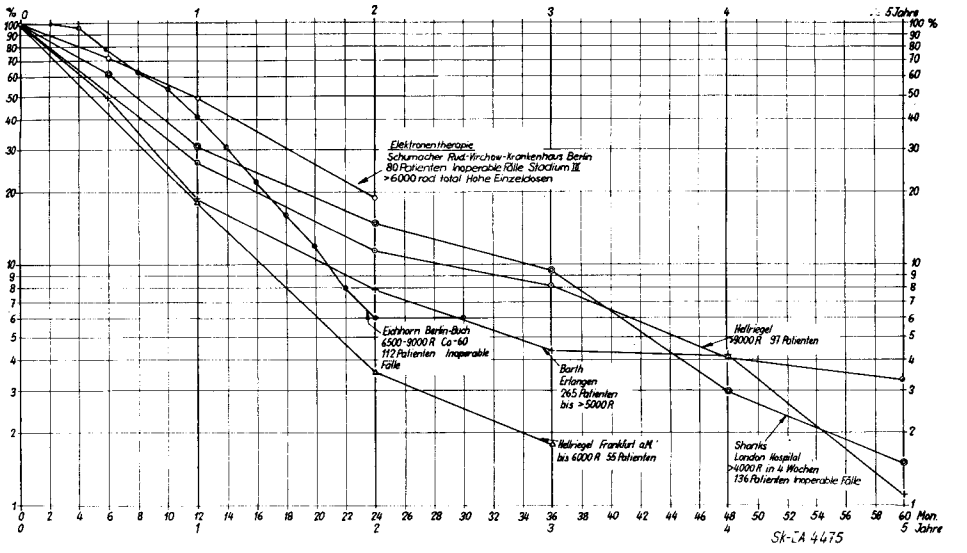

Fig. 2. A comparison of some results of radiation treatment of bronchial carcinoma. The conventional roentgen treatments show 1-year results with 20 to 30 % survivals (3-year results give less than 10 % survivals), whereas treatments with ^{60}Co rays give somewhat better 1-year results. So far the results with high-energy electrons using high single doses appear to be superior.

results than the commonly used daily doses of 200 to 300 rad with conventional roentgen or megavolt irradiation. The early treatment results are as good as for the operated patients (even when inoperable cases were treated), with one-year survival of about 50 %, as for patients of stages II and III. SCHUMACHER's results, and a comparison with other results of radiation treatments, are shown in Figs 1 and 2. (In the meantime, the results with a high single-dose treatment have been verified in other hospitals.)

Favourable results with high-energy electrons using conventional treatment doses have been reported by several hospitals (VERAGUTH 1961) with different cases. The good results may partly be due to a suitable dose distribution and a small integral dose (WIDERÖE 1959, 1961), but also specific biologic effects seem to make treatment with electrons more tolerable for the patients and lead to a favourable recovery of irradiated tissue. This makes it possible to administer much higher single doses with electrons than with other types of radiation.

For over 4 years now, in the Rudolf Virchow Hospital in Berlin (SCHUMACHER), single tumor doses of 500 to 600 rad given twice a week, or 1 000 to 1 200 rad given once a week, have been used. (With single doses of 1 000 to 1 200 rad, the first interval between irradiations is one week, the next interval

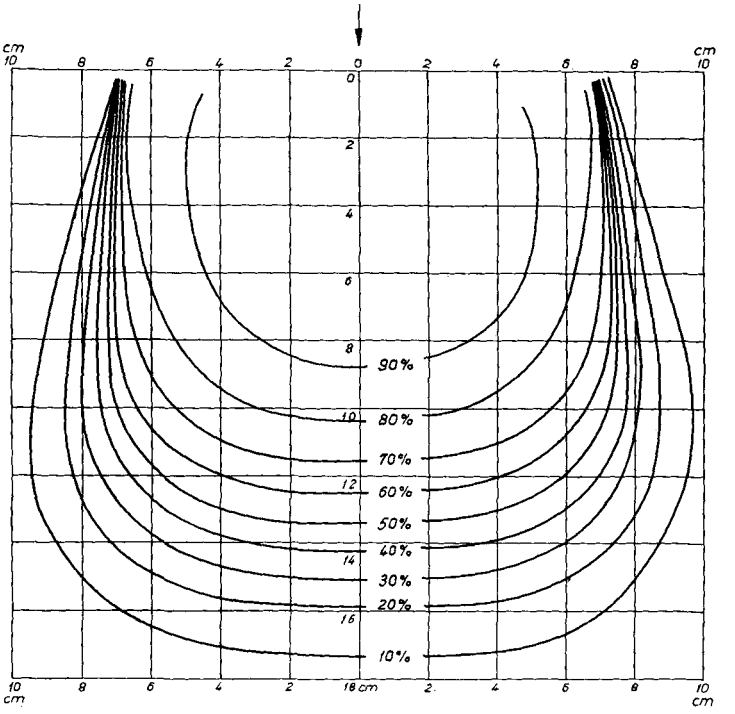

Fig. 3. Isodose curves measured in water for 35 MeV electrons with a (14 × 14) cm² field and at a 1.1 m focus-skin-distance.

two weeks and for further irradiations 4 weeks.) They lead to a rapid disappearance of the tumor; after 3 weeks, radiography of the lungs has shown definite improvement. The high single doses are tolerated remarkably well by the lung tissue, even in patients who are in a generally bad state (having for example abscesses, haemophtysa or lung tuberculosis). The irradiation in many cases causes radiation-pneumonitis which can be successfully treated with cortisone, calcium diuretin and antibiotics (DEELY 1960). It is necessary to have patients in this stage watched carefully and treated by a lung specialist, so as to avoid any false interpretation of the radiodiagnostic findings (LOERBROKS & SCHUMACHER).

Cell survival with high single doses will now be discussed. Isodose curves for 35 MeV electrons in water are given in Fig. 3, and in Fig. 4 the dose distribution in a 18 cm thick body treated contra-laterally with 35 MeV electrons is shown. The conditions might differ somewhat when the lung is irradiated; the density of the lung with air will be less; the thickness of the body

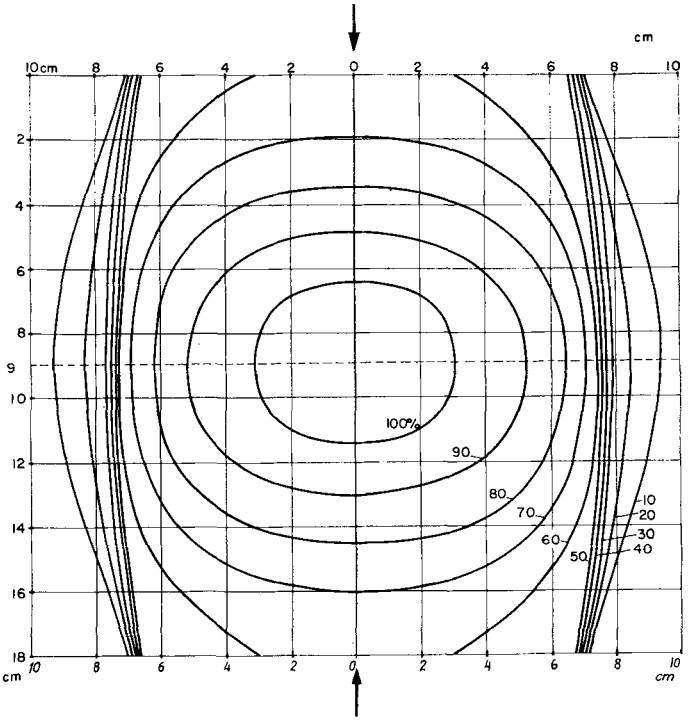

Fig. 4. Isodose curves in a water phantom of 18 cm thickness irradiated with 35 MeV electrons from two contra-lateral fields (14 × 14) cm², FSD = 1.1 m.

may be greater but the curves in Fig. 4 will grosso modo be typical for most of such treatments. Survival curves of heteroploid human kidney cells (T_1-cells), irradiated in cell cultures with roentgen rays and with electrons from ^{90}Y having a maximum energy of 2.18 MeV are given in Fig. 5.

The measurements made by BARENDSEN some years ago (1961) show the typical response of mammalian cells to irradiation. In a semi-logarithmic display the curves show a 'shoulder' for small doses while they are linear for large doses. If we apply the survival results of the kidney cells onto the dose distribution of Fig. 4, we get 'iso-survival' curves as shown in Fig. 6. On the left-hand side of the diagram the central single dose is 1 200 rad, on the right-hand side the single dose was taken to be 300 rad. From this we see that a single dose of 1 200 rad would kill more than 95 % of all cells at all depths in the body. The kidney cells are not especially radiosensitive, the sensitivity of

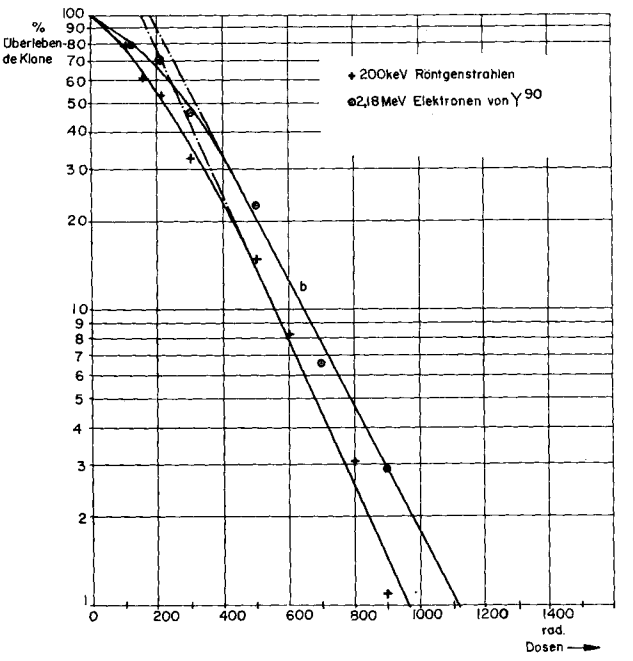

Fig. 5. Surviving, reproductive human kidney cells (T_1 cells) irradiated in cell cultures with 200 keV roentgen rays (HVL = 1.9 mm Cu) and electrons from ^{90}Y (2.18 MeV-max.) (BARENDSEN 1961).

the lung parenchyma should be at least equal. A single dose of 1 200 rad should therefore, roughly speaking, 'burn a big hole through the body' and why this does not happen remains to be explained.

At the Westminster Symposium in 1962 (see ref. 'Fractionation and Dose Rate') it was proposed (by Professor Ellis, and others) that the radiation damage stimulates the normal cells to step up proliferation to a very high rate, they repopulate the irradiated tissue by cell division and thus 'close the hole' in the interval between irradiations. — In this article we shall employ the terms 'regeneration' or 'repopulation' when the radiation damage is restored by division of the surviving cells, thus creating virtually the same tissue as before; the term 'repair' will be used when scar tissue is also produced after the radiation damage. — This explanation, however, seems quite unsatisfactory. A certain degree of repopulation may occur but a complete regeneration of such a major damage does not seem possible (see FOWLER, and STERN in 'Fractionation and Dose Rate'). We have to find other explanations for this dis-

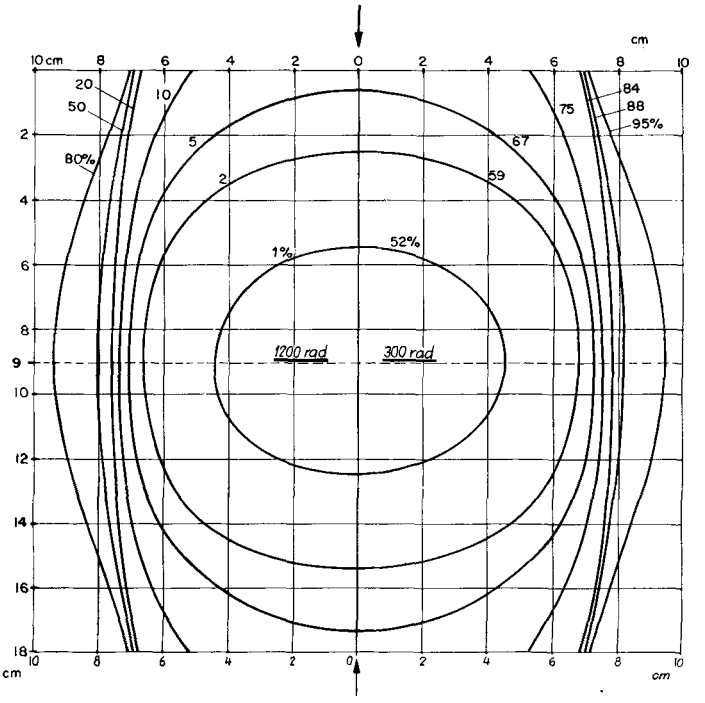

Fig. 6. 'Iso-survival' curves showing the surviving cells in a body irradiated contra-laterally with 35 MeV-electrons as in fig. 4, using the survival rates (for electrons) of fig. 5. On the left-hand side the single central dose is 1 200 rad, on the right-hand side the dose is 300 rad.

crepancy and, most probably, we have to look at the various recovery effects for the damage caused to cells in vitro and in vivo.

The primary radiation cell damage caused in vivo and in vitro is probably nearly the same, considering equal cytologic and ionizing conditions, but afterwards the roads divide. When a body is irradiated, recovery processes start; the body 'reservoirs' of enzymes and spare parts for production of proteins and other macromolecules are mobilized and a great deal of cell damage may be repaired, while cells in cultures without such recovery potentials die out. From this we learn that recovery processes, starting immediately after the irradiation, represent a very important secondary phase which in a high degree may decide the resulting 'radiosensitivity' of the cells in vivo. This recovery should of course not be confused with the short-time 'Elkind-recovery' acting in irradiated cell cultures which probably is based on the local intercellular recovery potential (Elkind & Sutton 1964).

When investigating mammal cultures of normal and tumor cells, we essentially find nearly the same radiosensitivity (differences up to a factor of 2 or 3 have been found: BARENDSEN 1964) and this is quite contrary to many cases in clinical radiotherapy where we have very great differences in radiosensitivity. This contradiction also shows clearly that the conditions in cell cultures must be very different from the situation in vivo where obviously the recovery phenomena are of decisive importance (HUG 1964).

The various attempts made in England and America to draw conclusions directly from cell cultures and relate them to radiotherapy, regardless of such recovery effects, would seem to be condemned to fail.

The amount and kind of radiation delivered to the cell is certainly of great importance. The primary damage is the starting point for all further processes, and the magnitude, type and intensity of the radiation are crucial for the recovery effects and for the results of treatment.

We will now develop a mathematical theory based on these ideas and thereby try to cover the radiobiologic as well as the therapeutic facts. It is our hope that such a theory might stimulate quantitative research in radiotherapy and thus lead to a better understanding and improved methods of treatment.

Radiobiologic and radiotherapeutic effects described by means of a two-component theory of radiation

The ion distribution in a cell irradiated with 200 rad of 30 MeV electrons is shown in Fig 7. The ions produced during the irradiation have been printed in the form of 440 small dots on an electron-microscopic image of a non-irradiated lymph node cell of a mouse (courtesy of GOLDFEDER 1962). The image measures (3.73×4.2) μ^2 and the slice is supposed to have a thickness of 0.13 μ. It will be hit by 32 high-energy electrons, crossing from left to right. With a commonly used dose rate of 200 rad per minute the slice of tissue which measures 0.545 μ^2 of surface (facing the electron beam), will be hit by one high-energy electron every 1.87 second. An accumulation of the effects from various primary tracks is therefore only possible for relatively long-lasting ionization effects.

More than 90 % of the ions produced by the high-energy electrons will be deposited as so called 'primary ions' very close to the track of the primary electron. These ions are fairly equally distributed, often 2 or 3 are found together in small clusters and the average density of the ionization is very low. In certain cases, however, the primary electron may also produce a secondary electron of such an energy (for instance: more than 700 to 800 keV) that it creates a separate track of ions (δ-ray) branching off from the track of the

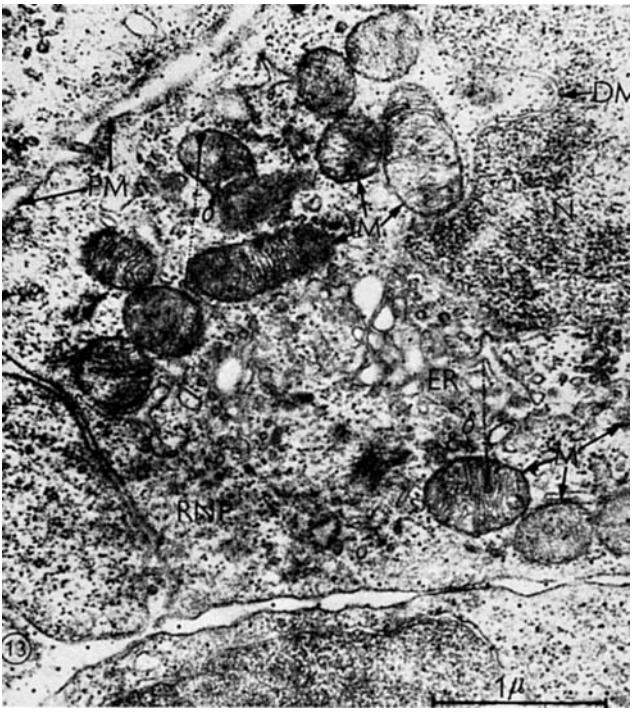

Fig. 7. Part of a lymph node cell of a mouse. PM is the plasma membrane surrounding the cell, ER the endoplasmic reticulum, RNP ribunucleose particles, M mitochondria and N the nucleus with its double membrane DM. A portion of another cell can be seen below; superimposed black dots are ions produced by 200 rad delivered by 30 MeV electron irradiation; δ are two secondary electrons with a joint energy of 9.6 keV. (Electron micrograph courtesy of GOLDFEDER 1962.)

primary ion track, and such a δ-track will end up in a bigger ion cluster containing about 22 ions in the last $\frac{1}{20}$ μ of the track. It is obvious, and it has often been mentioned (WIDERÖE 1960, ROSSI 1964) that such a concentrated group of ions will cause a much more profound and massive effect in the cell than the sparsely distributed primary ions. It even seems possible that a certain number of such δ-ion clusters hitting a sensitive part of the cell might cause fatal, non-reversible effects, such as a destruction of the nucleus or the membrane system, leading to acute or delayed death of the cell. With 30 MeV-electrons, relatively few such big ion clusters are produced but 30 MeV roentgen rays produce some more, and 200 keV roentgen rays a great many more (about 3 to 5 times as many), which shows that not only the strength of the dose but

also the type of radiation decides if an irradiated cell shall die out, be sterilized or recover.

BARENDSEN (1964), and others, have mentioned that every radiation can be considered as made up of various components each producing a different density of ionization (LET-value). In this way, the influence of fractionation, protraction, and oxygen pressure, on the survival of irradiated cell cultures can be explained. In order to link radiobiology with radiotherapy, we will now try to extend this idea to irradiations in vivo.

For the sake of simplicity, we suppose that the radiation is composed of only two components, a dense ionizing 'α-component' with high LET-values and a scarcely ionizing 'β-component'. The part of the total dose produced by the α-component will be designated a. Alpha rays with an energy of a few MeV (^{210}Po produces 5.3 MeV alpha rays) consist nearly entirely of an α-component ($a = 100$ %). Roentgen rays of 100 to 200 keV maximum energy probably contain an α-component of about 10 to 20 %, whereas 30 MeV roentgen rays may have a-values of 5 to 7 %, and 30 MeV electrons probably only 3 to 5 %. (The a numbers are estimated so as to suit radiobiologic measurements and also preliminary calculations on the number of δ-rays for various radiations.)

Investigations on irradiated cell cultures have established the dose/effect relations for the two components. The α-component gives an exponential relation of the number S_a of the surviving cells for a dose D

$$S_a = e^{-aD/D_{0a}} \tag{1}$$

where D_{0a} is the dose at which $S_a = 1/e = 36.8$ % of the cells survive. It does not seem possible to irradiate cells with an entirely 'clean' β-component (we always get some δ-electrons and consequently also a small α-component), and we shall therefore have to evaluate the dose effect relation for the solitary β-component from measurements with a mixed radiation, subtracting the influence of the α-component. In a semilogarithmic display, we then get the well known 'shoulder-curves' for the survival numbers due to the β-component which can be represented by the relation

$$S_\beta = 1 - (1 - e^{-(1-a)\,D/D_{0\beta}})^p \tag{2}$$

where p is the extrapolation number and $D_{0\beta}$ again the 36.8 % dose value for the linear part of the curve (semilogarithmic representation). Measurements by BARENDSEN (1961) have shown that the resulting number S_Σ of surviving cells will be the product of the survivals for the various components, which also means that the killing effects of the two radiation components are independent of each other. BARENDSEN measured the survival of cells irradiated by alpha rays and shortly after with roentgen rays. This should in principle not

Table 1

Cell survival (S_Σ) in vivo for normal cells as a function of dose (D)

$$S_\Sigma = e^{-\alpha D/D_{o\alpha}} \cdot \left[1 - \left(1 - e^{-(1-\alpha)D/k \cdot D_{o\beta}}\right)^p\right]$$

$D_{o\alpha} = 100$ rad, $D_{o\beta} = 200$ rad, extrapolation number $p = 3$, recovery factor $k = 5$ (normal cells)

$\alpha =$	$D =$	100	200	300	500	1 000	1 200	1 500	2 000 rad
0	$S_\beta = S_\Sigma =$	99.92	99.4	98.3	93.9	74.7	66.0	53	35.9 %
	$S_\alpha =$	96.95	93.8	91.4	86.0	74.1	69.7	63.8	54.9 %
	$S_\beta =$	99.92	99.45	98.38	94.3	76.0	67.6	55.2	37.0 %
3 %	$S_\Sigma =$	96.87	93.25	89.8	81.1	56.4	47.1	35.2	20.3 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	2.6	8.9	19.0	40.7	92.7	107	124	140 %
	$S_\alpha =$	95.0	90.6	86.0	77.9	60.6	54.9	47.2	36.8 %
	$S_\beta =$	99.92	99.49	98.48	94.55	76.7	68.6	56.5	38,0 %
5 %	$S_\Sigma =$	94.92	90.1	84.7	73.55	46.5	37.8	26.9	14.0 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	1.6	5.4	10.8	24.7	59.2	69.6	82.4	98 %
	$S_\alpha =$	90.5	81.9	74.1	60.6	36.8	30.1	22.3	13.5 %
	$S_\beta =$	99.93	99.55	98.68	95.25	79.1	71.0	59.2	42.0 %
10 %	$S_\Sigma =$	90.47	81.3	73.1	57.7	29.1	21.4	13.2	5.66 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	0.7	2.5	5.1	12.0	33.0	41.5	52.5	67.0 %
	$S_\alpha =$	86.0	74.1	63.7	47.15	22.3	16.55	10.53	4.98 %
	$S_\beta =$	99.95	99.62	98.85	95.87	81.3	73.8	62.7	45.4 %
15 %	$S_\Sigma =$	86.0	73.8	63.0	45.2	18.1	12.2	6.6	2.26 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	0.36	1.47	3.17	7.82	24.1	31.4	41.7	57.5 %
	$S_\alpha =$	81.9	67.0	54.9	36.8	13.5	9.1	4.98	1.91 %
	$S_\beta =$	99.96	99.68	99.02	96.4	83.4	76.5	66.0	49.1 %
20 %	$S_\Sigma =$	81.8	66.7	54.4	35.5	11.25	6.96	3.28	0.94 %
	$\frac{1-S_\beta}{1-S_\alpha} =$	0.25	0.97	2.04	5.7	19.2	25.8	35.8	51.9 %
100 %	$S_\alpha = S_\Sigma =$	36.8	13.5	4.98	0.667	0.0046 %	—	—	—

be different from a simultaneous irradiation with rays composed of two components

$$S_\Sigma = S_\beta \cdot S_\alpha \tag{3}$$

and thus for the total survival

$$S_\Sigma = e^{-\alpha D/D_{o\alpha}} \cdot \left[1 - \left(1 - e^{-(1-\alpha)D/D_{o\beta}}\right)^p\right] \tag{4}$$

Table 2

Cell survival (S_Σ) in vivo for tumor cells having a recovery factor $k = 2$, $D_{o\alpha} = 100$ rad, $D_{o\beta} = 200$ rad, $p = 3$, $1—S_\beta/1—S_\alpha$ = relation between the cells killed by the β-component and the α-component

α =	D =	100	200	300	500	1 000	1 200	1 500	2 000 rad
	S_α =	95.0	90.6	86.0	77.9	60.6	54.9	47.2	36.8 %
	S_β =	99.06	94.6	86.8	66.5	25.0	16.0	8.0	2.5 %
5 %	S_Σ %	94.1	85.6	74.5	51.8	15.1	8.8	3.78	0.92 %
	$\frac{1-S_\beta}{1-S_\alpha}$ =	18.8	57.5	94	152	190	186	174	154 %
	S_α =	90.5	81.9	74.1	60.6	36.8	30.1	22.3	13.5 %
10 %	S_β =	99.19	95.22	88.2	69.4	28.4	18.9	10.0	3.2 %
	S_Σ =	89.8	78.0	65.3	42.05	10.45	5.69	2.23	0.43 %
	$\frac{1-S_\beta}{1-S_\alpha}$ =	8.5	26.4	45.6	77.6	113	116	116	112 %
	S_α =	86.0	74.1	63.7	47.15	22.3	16.55	10.53	4.98 %
	S_β =	99.3	95.85	89.5	71.9	39.2	21.5	12.2	4.0 %
15 %	S_Σ =	85.4	71.7	57.0	34.0	7.1	3.56	1.29	0.20 %
	$\frac{1-S_\beta}{1-S_\alpha}$ =	5.0	16	29	53.2	78.3	94	98	101 %
	S_α =	81.9	67.0	54.9	36.8	13.5	9.1	4.98	1.91 %
20 %	S_β =	99.4	96.4	90.8	74.8	35.0	25.0	14.0	5.5 %
	S_Σ =	81.3	64.6	49.8	27.5	4.72	2.28	0.7	0.105 %
	$\frac{1-S_\beta}{1-S_\alpha}$ =	3.5	11.3	20.4	40.0	75.2	92.7	90.5	96.3 %

In the following discussion, we will suppose $D_{o\alpha}$ to be 100 rad (corresponding to a LET-value of about 57 keV/μ) and $D_{o\beta}$ to be 200 rad with an extrapolation number $p = 3$. With these values, we get survivals for $\alpha = 100$ % (alpha rays from ^{210}Po) and $\alpha = 15$ % (200 keV$_m$ roentgen rays) which correspond well to the measurements of BARENDSEN (1964).

We now postulate, when irradiating cells in vivo, that to satisfy the clinical experience, the dose constant D_o has to be multiplied by a recovery factor k (also the extrapolation number p might change but in order to simplify the mathematics we have neglected such effects; a refinement of the theory may perhaps be necessary later). Cell cultures irradiated with alpha rays do not show any short-time recovery ('Elkind-recovery') (ELKIND et coll. 1964). We therefore suppose that the α-component will only be submitted to an insignificant recovery effect and consequently take $k = 1$. However, for the β-component, we choose $k = 5$ for normal cells (i.e. $kD_{o\beta} = 1\,000$ rad) and $k = 2$ for tumor cells (i.e. $kD_{o\beta} = 400$ rad). These values may seem somewhat

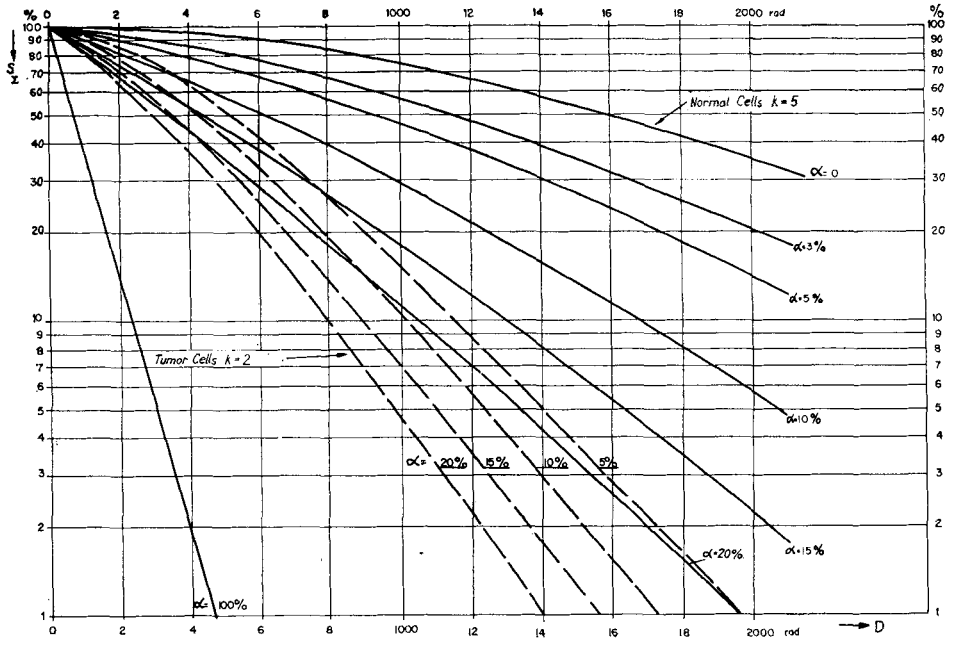

Fig. 8. Calculated survival numbers S_Σ for cells irradiated in vivo as a function of dose for various kinds of radiation (see also Tables 1 and 2). The ordinate is logarithmic, the abscissa linear.

arbitrary (the recovery factor k may also differ greatly for different cells) but they have been chosen to make the survival numbers consistent with the clinical experience.

In Tables 1 and 2, as well as in Fig. 8, the survivals in vivo are shown for various α-values and various doses (single doses), calculated with these parameters.

To-day, most people agree that recovery effects in vivo are essential for a successful tumor therapy, and the importance of the tumor bed, i.e. the normal cells surrounding the tumor cells, for the results of therapy, is generally accepted. It has often been mentioned that differences in the recovery of tumor cells and normal cells after radiation damage may improve the electivity of the radiation (COHEN 1960). Our theory, and the values chosen for the recovery factor k, give only a mathematical formulation of such ideas. The relation between surviving numbers of the normal cells and of tumor cells is shown in Fig. 9.

With small doses where the α-component, showing no recovery, is producing the greatest effect, this relation is very close to 1. When, however, the dose is increased for instance above 500 rad, the influence of the β-component gains

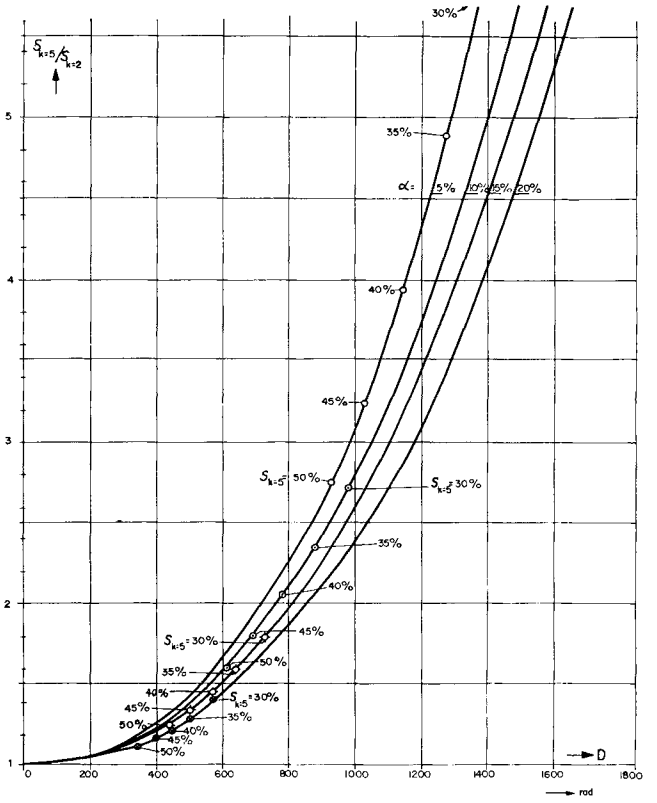

Fig. 9. Relation ($S_{k=5}/S_{k=2}$) between the surviving normal and the surviving tumor cells depending on the magnitude of the single dose. The relation (electivity) was calculated with the survival numbers shown in fig. 8 and Tables 1 and 2. The curves show the calculated electivity for various quota α of the α-component. Survival numbers from 30 to 50 % for irradiated normal cells are marked on the curves. Ordinates and abscissa linear.

in importance and the electivity relation will increase. With $\alpha = 5$ % (irradiation with 30 MeV electrons), a dose of 1 000 rad gives an electivity relation of 3.1, whereas higher α-values result in a somewhat smaller electivity. When comparing the values for the various types of radiation, however, we have to pay due attention to the fact that the size of the applicable single doses is limited because of the tolerance of the patient. The number of surviving normal cells after irradiation may be taken as a limit for the size of dose that can be applied. If this number drops below, let us say 30 to 50 %, the repopulations of the tissue with new cells, in the interval between two irradiations, may be insufficient and thus result in a non-tolerable radiation damage.

Table 3

Factor of electivity $S_{k=5}/S_{k=2}$ as a function of dose (D) for various values of α and the same parameters as for tables 1 and 2

α	D =	100	200	300	500	1 000	1 200	1 500	2 000 rad
5 %	$S_{k=5}/S_{k=2}$ =	1.008	1.052	1.136	1.419	3.08	4.3	7.12	15.2
10 %	=	1.0075	1.042	1.120	1.372	2.78	3.77	5.92	13.4
15 %	=	1.007	1.029	1.105	1.33	2.55	3.43	5.12	11.3
20 %	=	1.006	1.032	1.091	1.29	2.38	3.05	4.69	8.95

In Fig. 9 (see also Table 3), we have marked on the curves the dose values for which we get 30 to 50 % surviving normal cells. If we take, for example, 40 % as a limit, the maximum permissible single dose will be 1 150 rad for high-energy electrons ($\alpha = 5$ %), giving an electivity relation of nearly 4, whereas 200 keV roentgen rays ($\alpha = 15$ %) will allow of only a 570 rad single dose to be given which results in an electivity of only 1.45.

These results very clearly disclose two facts: first, the important therapeutic advantages of high single doses, and secondly, the benefit of therapy with high-energy electrons. Single doses of 300 rad are used quite often. In this case, the electivity is only 1.2, and the recovery effects of the normal cells are then of little influence because most of the cells are sterilized by the α-component of radiation. In Tables 1 and 2, also the relations of the cells killed by the β-component are quoted, i.e. $(1-S_\beta)$ to those killed by the α-component, i.e. $(1-S_\alpha)$. If we use a single dose of 300 rad, the relation $\frac{1-S_\beta}{1-S_\alpha}$ for normal cells is only 2.04 % for $\alpha = 20$ %, and 10.8 % for $\alpha = 5$ %, thus showing that in these cases the influence of the α-component predominates. A single 1 200 rad dose of high-energy electrons ($\alpha = 5$ %) will in contrast give a relation of 70 %, and in this case the β-component can certainly not be disregarded.

At the body-depth of the tumor, where most of the high-energy electrons have been attenuated to lower energies, the α-value will be higher of course and the α-component will thus have a greater influence. For $\alpha = 10$ %, a single dose of 1 200 rad for instance will give a relation $\frac{1-S_\beta}{1-S_\alpha}$ of 41.5 % for normal cells and 116 % for tumor cells.

We will now discuss the relative numbers of surviving tumor cells for various radiations and treatment plans. The numbers of surviving tumor cells, with a single dose of 200 rad, and also for $n = 30$ single doses given ($D_{total} = 6\,000$ rad) as fractionated treatment for various values of α, are given in Table 4.

Table 4

Survival rate (S_Σ) for tumor cells with a recovery factor k = 2 for various values of α and a single dose of 200 rad and also 30 separate doses of 200 rad (total dose 6 000 rad) — Parameters are the same as for tables 1 and 2

	$\alpha = 5$	10	15	20 %
$D_1 = 200$ rad	$S_\Sigma = 85.6$	78.0	71.7	64.6 %
$D_{total} = 30 \times D_1 = 6\,000$ rad	$S_\Sigma = 942 \cdot 10^{-5}$	$47.8 \cdot 10^{-5}$	$4.63 \cdot 10^{-5}$	$0.203 \cdot 10^{-5}$

With 200 keV roentgen irradiation ($\alpha = 15$ %) a total dose of 6 000 rad is used in many cases, and we will therefore take the survival number $S_\Sigma = (0.717)^{30} = 4.63 \cdot 10^{-5}$ for this case as a typical end-point for classical radiotherapy (this does of course not exclude the fact that a still smaller number of tumor cells would be very desirable). The fractionation number n is now easy to calculate as well as the total dose $n \cdot D_1$ which, using high-energy electron therapy with $\alpha = 10$ %, will give the same survival figure ($4.63 \cdot 10^{-5}$) of tumor cells for various single doses. These values are shown in the upper line of Table 5. If the single dose is 200 rad, the total dose with electron therapy should be 8 040 rad, and this value corresponds very well with to-day's practice. Single doses of 1 200 rad give a total dose of 4 170 rad, in good agreement with SCHUMACHER's experiences (1964). The calculated values in Table 5 show exactly the same trend as the total doses found experimentally by STRANDQVIST (1944) with fractionated irradiation of skin and squamous carcinoma cells using conventional roentgen irradiation.

The calculated survivals will of course not apply to anoxic tumor cells. The oxygen effect will change the sensitivity of the cells with regard to the β-component whereas the influence of the α-component will probably change very little. — Measurements on cell cultures show (according to BARENDSEN 1964) that the D_0-value for ^{210}Po alpha rays will increase only 18 % for cells in nitrogen, as compared to cells in air. Measurements in vivo are lacking. — If we assume that the killing by the α-component remains unchanged, whereas the D_0-value for the β-component increases by a factor of 2.5 for anoxic cells, we will get the same survival numbers for the anoxic tumor cells as previously calculated for normal cells (Table 1). The criterion for the survival number of the anoxic tumor cells with 200 rad single dose and $\alpha = 15$ % (i.e. conventional roentgen therapy) will then be $S_\Sigma = (0.738)^{30} = 11.01 \cdot 10^{-5}$, and using this value we now get much higher values for the fractionation numbers n and for the

Table 5

Number of irradiations (n) and total dose (D_{total}) necessary to reduce the surviving tumor cells to a fraction of $4.63 \cdot 10^{-5}$ for oxygenated cells with a recovery factor $k = 2$, and to $1.10 \cdot 10^{-4}$ for anoxic tumor cells having $k = 5$ (D_1 is the single dose given) — Parameters same as for previous tables

$k =$	$D_1 =$	100	200	300	500	1 000	1 200	1 500	2 000 rad
	n =	92.7	40.2	23.4	11.5	4.44	3.47	2.61	1.57
2	D_{total} =	9 270	8 040	7 020	5 760	4 440	4 160	3 920	3 140 rad
	n =	91.0	44.0	29.05	16.58	7.38	5.91	4.50	3.17
5	D_{total} =	9 100	8 800	8 720	8 290	7 380	7 090	6 750	6 340 rad

total doses D_{total} with electron therapy as before (see Table 5, lower lines). Single doses of 200 rad will for instance give a total dose of 8 800 rad whereas single doses of 1 200 rad result in a total dose of 7 090 rad. However, we have to remember that only a small part (perhaps only 10 %) of the tumor cells might be anoxic, and the criterion of survival, $11.01 \cdot 10^{-5}$, is therefore now much stronger and much more difficult to fulfill than the criterion in our previous example for oxygenated tumor cells. To-day, our experiences with high-energy electron therapy using high single doses are still too young to demonstrate the necessity of such high total doses; however, there are some indications from SCHUMACHER's results that higher total doses must be given to avoid local recurrences. In this connection, hyperaemic effects, e.g. supervascularisation, with an increased oxygenation caused by the high single dose also have to be taken into the consideration.

These few examples show that a two-component theory of radiation, considering the recovery effects of cells in vivo, can give quantitative explanations and useful answers to many problems in radiation therapy. It has to be remembered, however, that we have used hypothetical parameters for our calculations, and in order to develop our hypothesis into a well-founded theory those parameters have to be measured.

The relation α for various radiations may be relatively easy to measure. ROSSI's low-pressure proportional-counter (1961) could be useful, calculations of the number of δ-rays may give indications (HUG 1964, ROSSI 1964) (again the lowest energy defining a δ-ray is important) and perhaps also some radiobiologic tests, for instance radiation-induced chromosome alterations which only show up for the α-component (NEARY et coll. 1963) may be helpful. Such measurements must be carried out at various depths of a phantom and in future therapy work not only isodose curves but also iso-α-curves will be necessary to characterize the dose field in a body, especially when more than one treatment field is used. The measurement of the α-values is an entirely

physical task. However, the definition of the α-component for various types of radiation must be based on biological experience and measurements. — In order to explain all experiences with cell cultures, BARENDSEN has proposed to divide the spectrum of radiation into three parts with various LET-values: below 20 keV/μ, between 20/100 keV/μ and above 100 keV/μ. — The sparsely ionizing part may correspond with our β-component whereas our α-component now has been divided into one part that depends on oxygen pressure and cysteamine treatment and another part (LET above 100 keV/μ) that is independent of such influence. When measurements in vivo have been further developed, allowing quantitative measurements of cell survivals, our present theory will perhaps have to be further refined; also tumor growth during the treatment period will have to be considered.

Of equal importance is the quantitative measurement of the biologic effects in vivo. To-day, radiotherapists mostly use more or less qualitative indications of the radiation effects (lysis effects on tumors, skin erythema) or some indirect effects (changes in rate of mitosis, (REICHE 1955), changes in chemical cell reactions (ZUPPINGER & MINDER 1962), changes in the mass of an organ (OESER 1962) and change in protein production of the cells). However, such indirect effects may often be influenced also by other causes. Only a reliable and fairly exact method for registering 'survival in vivo' will enable quantitative investigations of recovery effects in vivo to be made.

In our calculations we have treated the recovery effect in a very cursory and simplified way (recovery factor k). Very probably the recovery may be the result of many complicated phenomena that may depend on time, milieu, cell type, the general condition of the patient, immunologic reactions and, last but not least, on the various parameters of irradiation (we have for instance not mentioned the important and not very well understood influence of the dose rate).

Our philosophy has shown that the phase of recovery in many cases may be decisive for the successful treatment of the patient. The electivity can be increased by a suitable irradiation rythm but certain limits of the single doses must not be surpassed in order to avoid serious radiation injury. Physical problems such as dosimetry, and the planning and application of a suitable dose field are, more or less, trivial problems for the therapist and could in many cases be left to the radiation physicist, whereas the study and investigation of the biologic problems in vivo, mainly the recovery phase and the immunologic reactions, should be the most important fields for the physician.

There are at present many investigators who study the influence and the combined use of chemical agents (cytostatica, enhanced oxygen pressure and the like) on radiation therapy, and also on the recovery phase (injection of

radioprotective drugs, such as pyridoxal-5-phosphate, vitamin B_{12} and anabolic steroids). It seems clear that cytostatica could adversely influence the recovery of the normal cells and also depress such immunologic reactions of the body that are specially important for the elimination of metastases. This assumption has recently been confirmed clinically. An elevated oxygen pressure, and also 'radiation-protective' drugs, may on the other hand advance recovery and therefore be helpful ('recovery treatment'). Such indications will be especially important when high single irradiation doses are used. Again we have to remember that quantitative investigations of such effects require exact measurements of cell survival in vivo.

Our theory is an attempt to bridge the existing gap between radiobiology and radiotherapy without too much speculation upon the still very hypothetical ideas concerning the primary radiation effects on the macromolecules of the cells. It lies, of course, near at hand to identify the influence of the α-component as a hit and injury of the cell nucleus (i.e. nucleic acids), whereas the influence of the β-component probably depends on the accumulation of many single ionization effects causing damage to sensitive structures over the entire cell volume.

SUMMARY

Clinical experience shows that survival curves obtained with irradiated cell cultures are not directly applicable to therapeutic irradiations. The inconsistency may be due to different recovery effects for conditions in vitro and in vivo. For a mathematical investigation radiation is divided into a densely ionizing 'α-component' producing exponential dose-effect curves and a sparsely ionizing 'β-component' producing 'shoulder-curves'. It is postulated that the 37 % dose for the β-component (linear part of the curve) is increased by a recovery factor k for cells in vivo as compared to cell cultures. An example is given, showing that curve parameters may be chosen so as to agree with results in vitro as well as with radiotherapeutic experience. Therapy with high-energy electrons having only a small part of the α-component (α about 5 %) gives the best recovery and superior treatment results, especially when high single doses, resulting in increased electivity, are used.

ZUSAMMENFASSUNG

Klinische Erfahrungen zeigen, dass die Ergebnisse der bestrahlten Zellkulturen sich nicht ohne weiteres auf die Strahlentherapie übertragen lassen. Die Unterschiede lassen sich durch unterschiedliche Erholungseffekte in vitro und in vivo erklären. Für eine mathematische Untersuchung wird die Strahlung in eine dicht ionizierende 'α-Komponente' und eine spärlich ionizierende 'β-Komponente' zerlegt. Die α-Komponente (Anteil α) erzeugt exponentielle Dosiseffekt-Kurven, die β-Komponente 'Schulterkurven'. Es wird postuliert, dass die 37 % Dosis der β-Komponente (im linearen Kurventeil) durch Erholungseffekte in vivo gegenüber die Verhältnisse in vitro um den Faktor k erhöht wird. Ein Beispiel zeigt, dass die Parameter so gewählt werden können, dass die Resultate mit den Zellkulturmessungen und

auch mit den strahlentherapeutischen Erfahrungen übereinstimmen. Hochenergetische Elektronen haben den kleinsten Anteil (~ 5 %) an der α-Komponente. Dies erklärt die gute Erholung nach der Bestrahlung. Wenn hohe Einzeldosen verwendet werden, steigt die Elektivität der Bestrahlung und die therapeutische Ergebnisse werden besser.

RÉSUMÉ

L'expérimentation clinique montre que les courbes de survie des cultures de cellules irradiées ne sont pas directement applicables aux irradiations thérapeutiques. On peut expliquer cette discordance par une différence des effets de restauration in vitro et in vivo. Pour traiter ce problème de façon mathématique on divise les radiations en deux groupes: une composante alpha à haute densité ionisante donnant des courbes exponentielles de l'effet en fonction de la dose, et une composante béta à faible pouvoir ionisant donnant des courbes en forme d'épaulement. L'auteur émet le postulat suivant : la dose constante D_0 (pour 37 % de survivants) pour la composante béta (partie linéaire de la courbe) est multipliée par un facteur de restauration k pour les cellules in vivo par rapport aux cultures de cellules. Il donne un exemple montrant qu'on peut choisir les paramètres de courbes de façon que les resultats in vitro correspondent avec l'expérimentation thérapeutique. Les électrons de grande énergie n'ont qu'une très faible composante alpha, environ 5 %. Ceci explique qu'ils permettent une meilleure restauration et donnent des résultats thérapeutiques supérieurs, en particulier quand on donne une forte dose unique qui augmente l'électivité de l'irradiation.

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