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EFFECTS OF FRACTIONATED DOSES OF ELECTRONS ON HUMAN SKIN

by

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Recent data on the survival and recovery of mammalian cells (BARENDSEN et coll. 1963, HEWITT & WILSON 1959, KALLMAN et coll. 1964, SILINI & METALLI 1966) have indicated that the dose-time relationship for a given fractionation schedule may be more specifically expressed by the relationships between (1) the total dose and the dose per fraction (i.e. total dose/number of fractions) and (2) the total dose and the time interval between repeated equal fractions.

The work of FOWLER et coll. (1965) on pig skin erythema and desquamation revealed that the dose value per fraction plays a greater role than the time interval between fractions. The variation in total dose with total fractionation time is small but not negligible, and has been discussed by ELLIS (1967), FOWLER (1965, 1968) and SPRING & HOLMBERG (1968). The present clinical investigation takes into account only the first of the two relationships, leaving aside time factors, such as the interval of time between fractions and the total fractionation time.

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Material. The investigation was based on the evaluation and comparison of early and late skin reactions. Patients with mammary carcinoma undergoing radiation therapy after surgical treatment were examined over a period of eight months. The effects of different dose fractionation schedules were evaluated by comparing skin reactions of both parasternal sides of the same patient. Irradiation was carried out with 15 MeV electron beams to 4 cm $\times$ 12 cm areas.

Dosimetry was performed by means of an ionisation and extrapolation chamber (BELLETTI & TORNIELLI 1964), whereas the dose distribution on both parasternal sides was determined by photographic films.

Evaluation of skin reaction. The right parasternal side of each patient was used as a control field and irradiated according to a constant fractionation schedule. The comparison between two different fractionation schedules was carried out on the same patient. This was to avoid variability due to the differing sensitivities of different patients, as indicated by varying magnitudes of reactions or differing times of their appearance.

Early skin reactions were evaluated by three different stages of erythema: initial, florid and purple, numbered 1, 2 and 3, respectively. The most reliable evaluation was obtained when the erythema reached the second stage; initial and purple erythema lead sometimes to equivocal conclusions. Among the late reactions were the appearance of dyschromias, skin atrophy, teleangiectasis and sclerosis of the subcutaneous tissues. Early reactions were checked 20 to 24 hours after each fraction, whereas late reactions were controlled weekly, starting 3 to 4 months after the end of radiation therapy. Experience in the use of electrons together with that of other authors (TRUCCHI 1960), established that for electrons the erythema characteristics of the doses given appear within 24 hours without the necessity of waiting a greater length of time. The evaluation of early and late reactions was carried out independently by 4 to 5 different observers. The indications supplied by the majority of the observers were considered valid.

Fractionation schemes. Only the influence of the 'dose per fraction' was intended to be taken into account leaving out the influence of the time interval between fractions.

Fractions of varying doses (150, 250, 300 rad) were delivered to the left parasternal side and a constant fraction of 200 rad to the right parasternal side (Table 1). Daily doses up to those values are commonly used in clinical practice and are given for five days a week with the usual interval of two days between each cycle of five irradiations. The investigation also took into account higher dose values per fraction (400, 600, 1 000 rad). The time interval of such high doses (and for the 300 rad doses) was increased to 2, 3 and 7 days, respectively,

Table 1

Fractionation schemes

Dose per fraction (rad/interval)		No. of patients
Left parasternal side	Right parasternal side	
150 daily	200 daily	12
250 daily	200 daily	10
300 daily	200 daily	12
300/2 days	200 daily	8
400/2 days	200 daily	10
600/3 days	200 daily	8
1 000/7 days	200 daily	4

Table 2

Method of obtaining the value of the fractionation factor

No. of patients	Dose to right side	Dose to left side	Ratio
1	a_1	b_1	b_1/a_1
2	a_2	b_2	b_2/a_2
3	a_3	b_3	b_3/a_3
n	an	bn	bn/an

$$\text{Fractionation factor of X rad/day} = \frac{\sum_{1}^{N} b_n/a_n}{N}$$

in order to avoid overdose reactions. This procedure also allowed useful information on the use of high doses in the clinical field to be obtained.

Late reactions were investigated at 90 and 120 days from the end of treatment by varying, within the usual therapeutic dose range, the total dose for the 200 rad/day scheme (on the right parasternal side). This represented the reference fractionation, and held constant the total dose for the various fractionation schemes under test (on the left parasternal side). Several groups of patients were selected for every fractionation scheme with a total constant dose on the left side for each group, but variable from group to group (300 to 200 rad/day in four groups of patients with total doses constant for each group of 3 600, 3 600, 3 900, 3 300, respectively) (Tables 3, 4). The two total doses for every group of patients that will eventually induce the same late reaction on both sides may be estimated.

Fractionation factor. The ratio between the two doses found to be necessary to produce equivalent effects in both the test fields of a given patient, yields an index of the relative efficiency of the two fractionation schemes in causing the early or late reactions. One of these fields received the fractionation under test and the other the 200 rad/day reference fractionation. A series of values of this ratio (each one pertaining to a single patient) is obtained from each group of patients treated with the same fractionation scheme. The average is a dose modifying factor due to fractionation: this will be termed 'fractionation factor' for brevity.

The method of obtaining the value of the fractionation factor appears in Table 2 (200 rad/day, right side compared to X rad/day, left side).

Dose a_n and b_n refer either to the appearance on both sides of an equal grade of erythema (stages 1, 2, 3) during treatment or to the appearances of a similar type of late reaction on both sides 90 to 120 days from the end of treatment. The values of a_n and b_n for erythema and late reactions due to the different fractionation schedules are reported, together with the resulting values of the fractionation factor, in Tables 3 and 4.

It is necessary to remember that late reactions are associated with alterations not only in the epidermis or dermis but also in the underlying subcutaneous tissues. The appearance of these alterations after a given dose treatment does not follow constant progression and association, because of different individual sensitivity. A particularly late reaction was not therefore considered but since the comparison was performed in the same patient, the two different fractionations and the two different total doses were assumed to be equivalent when the late reaction appeared to be the same on both sides of the patient.

Results

The data for early and late reactions appear together in Fig. 1 although for convenience they will be discussed separately.

Erythema. The values of the fractionation factor for erythema were plotted against the dose per fraction; the 'daily' dose of 200 rad per fraction was used as reference (Fig. 1, Table 1). A continuous curve was drawn up to the experimental point at 400 rad and extended as a original/broken curve at higher doses, since reliable fractionation factors for erythema are not available at these levels. In fact, the values obtained at doses higher than 400 rad per fraction may be unavoidably affected by the large difference in total dose between two successive numbers of fractions. For instance, with the 600 rad per dose fractionation method, the progression is 600, 1 200, 1 800, 2 400 rad (*b* in Table 2) which, compared to the progression of the 200 rad per dose in standard frac-

Table 3

The dose values for erythema in the three stages of intensity: initial, florid and purple (stage 1, 2, 3) in both parasternal fields. Each line and each comparison is derived from one patient. The stage, the dose in both fields and the dose ratio are indicated for each patient. The values of the fractionation factors also appear.

200/day—150/day				200/day—250/day				200/day—300/day			
Stage	Right side dose	Left side dose	Ratio	Stage	Right side dose	Left side dose	Ratio	Stage	Right side dose	Left side dose	Ratio
2	2 000	2 400	1.200	2	2 400	2 000	0.833	2	2 700	2 200	0.815
2	2 200	2 850	1.295	2	2 000	2 000	1.000	2	1 800	1 500	0.833
2	1 400	1 800	1.285	3	3 200	3 000	0.937	3	2 600	2 400	0.923
3	3 200	3 600	1.125	3	3 000	2 800	0.933	1	1 000	900	0.900
2	2 000	2 250	1.125	1	1 200	1 000	0.833	2	3 000	2 400	0.800
2	2 200	2 400	1.090	2	2 200	2 000	0.909	1	1 000	900	0.900
2	1 600	2 100	1.312	2	1 800	1 750	0.972	2	2 800	2 400	0.857
2	2 000	2 250	1.125	3	2 600	2 500	0.961	1	1 200	900	0.750
1	1 000	1 200	1.200	2	2 000	1 750	0.875	2	2 900	2 700	0.931
3	3 200	3 600	1.125	2	2 200	2 000	0.909	2	2 900	2 400	0.827
1	1 200	1 500	1.250					1	1 500	1 200	0.800
2	2 200	2 700	1.227					2	2 300	2 100	0.913
Fractionation factor				Fractionation factor				Fractionation factor			
1.196 ± 0.072				0.916 ± 0.056				0.854			

Mean fractionation factor between 200/day—300/day and 200/day—300/2 days is 0.840 ± 0.058.

tionation (a in Table 2), produces values of b/a ratio separated by a large interval; the error affecting the fractionation factor, already significant for the 400 rad fractionation method, would then become so large as to deprive the calculated value of its meaning (Fig. 1).

Late reactions. The fractionation factors for late reactions appear in Fig. 1. It was impossible to calculate the error of the experimental points, since with the staging method it would have needed an impractically large number of patients to obtain sufficient fractionation factors. Research was therefore limited to one value of the fractionation factor for every patient, following the staging technique mentioned above. The spread of values is indicated in Table 4.

A comparison between fractionation factors for erythema and late reaction discloses a similar trend so that it appears that the fractionation factor is the same in the case of early and late reactions. This finding agrees with that of FOWLER et coll. (1963, 1965) in pig skin. On this assumption the curve of

Table 3 *(cont.)*

200/day—300/2 days				200/day—400/2 days				200/day—600/3 days			
Stage	Right side dose	Left side dose	Ratio	Stage	Right side dose	Left side dose	Ratio	Stage	Right side dose	Left side dose	Ratio
1	1 300	1 050	0.810	1	1 000	800	0.800	2	3 000	—	—
1	1 000	900	0.900	3	1 800	1 200	0.667	3	2 200	1 800	0.820
2	1 800	1 500	0.833	2	1 400	1 200	0.857	2	2 000	1 200	0.600
1	1 200	900	0.750	1	1 400	1 200	0.857	2	2 200	1 200	0.681
										1 800	0.818
2	2 400	1 800	0.750	2	2 000	1 600	0.800	2	2 200	1 200	0.681
										1 800	0.818
2	2 000	1 800	0.900	1	1 200	800	0.667	3	2 600	—	—
2	1 600	1 200	0.750	2	2 000	1 400	0.700	2	1 800	1 200	0.667
3	2 800	2 400	0.857	2	1 600	1 200	0.750	3	2 800	—	—
				3	2 000	1 600	0.800				
				3	2 600	2 000	0.769				
Fractionation factor 0.818				Fractionation factor 0.767 ± 0.070							

erythema was extrapolated up to 1 000 rad per fraction, making use of the fractionation factors for late reaction obtained at higher doses.

Knowledge of the average value of the dose causing erythema for a given fractionation scheme enables the results to be plotted as a curve on which the erythema dose was plotted against the number of fractions. The average value of the erythema dose measured in 64 patients on the right-hand parasternal 'control' side, was 2 100 rad for a fractionation method of 200 rad/day, i.e. 10.5 fractions of 200 rad each given 'daily'. This value and the fractionation factors in Fig. 1, produced an iso-effect curve for 15 MeV electrons referring to a 4 cm $\times$ 12 cm area (Fig. 2, curve 1). A reference curve S has been plotted on the same graph; this represents the iso-effect curve for erythema obtained by STRANDQVIST with conventional roentgen radiation. Although no correction for dose or RBE has been applied, the absolute values of the two curves are in reasonable agreement (assuming an RBE for the electrons of less than unity would bring them into better agreement) although their shapes appear to be different. The value of 1 350 rad is the extrapolated equivalent dose for erythema obtained by drawing curve 1 (Fig. 2).

Table 4

The pairs of total doses that induce equivalent reactions at 90 to 120 days from the end of treatment are given for late reactions. The dose range produced matched reactions in both parasternal fields; the values of the resultant fractionation factor are stated.

	200/day—300/day			200/day—400/2 days		
	Right side dose	Left side dose	Ratio	Right side dose	Left side dose	Ratio
	4 200	3 600	0.857	4 200	3 200	0.761
	4 400	3 600	0.818	4 400	3 200	0.727
	4 600	3 900	0.847	4 200	3 200	0.761
	4 000	3 300	0.825			
Dose Range	4 000 — 4 600	3 300 — 3 900		4 000 — 4 600	3 200 — 3 600	
Fractionation factor	0.836 ± 0.018			0.749 ± 0.020		

Conclusions

A comparison between the two-effect curve for erythema obtained in the present series of experiments and the theoretic curves derived from research in experimental radiation biology is interesting. Such curves were previously obtained and analysed by FOWLER & STERN (1963). These authors, on the basis of mammalian cell survival curve reported by HEWITT & WILSON (1959), PUCK & MARCUS (1956), ELKIND & SUTTON (1960), BARENDSEN et coll. (1960), used values of D_0 and n of 130 rad and 2.8, respectively. It has, moreover, been noted (NIAS 1963) that small variations in these values introduce insignificant changes in the iso-effects curve.

The curves used by FOWLER & STERN have been plotted for this comparison in Fig. 3. It should be noted that the ordinate of this graph is the ratio D_n/D_1 (where D_1 represents the dose necessary to obtain certain effects with a single fraction and D_n is the total dose for n fractions) and this is plotted against the number of fractions n. This plot takes into account only the shape of the curve without consideration of the actual dose value given by D_1. Only two of the iso-effects curves drawn by FOWLER & STERN appear in Fig 3; curve a with a D_1 of 1 040 rad and curve b with a D_1 of 1 500 rad. These values of D_1 appear

Table 4 *(cont.)*

200/day – 600/3 days			200/day – 1000/7 days		
Right side dose	Left side dose	Ratio	Right side dose	Left side dose	Ratio
4 000	3 000	0.750	3 200	2 000	0.625
4 200	3 000	0.714			
3 800 – 4 600	3 000		3 200 – 3 800	2 000	
0.732 ± 0.025			0.625		

to allow a comparison to be made with an iso-effect curve for erythema. Curve 1 in Fig. 3 is that obtained by the present authors and curve S represents the results of STRANDQVIST. It may be deduced from the data in Fig. 2 that curves 1 and S demand that the values of D_1 should be 1 350 rad and 1 000 rad, respectively, and that the experimental and theoretic values of D_1 are thus almost equal.

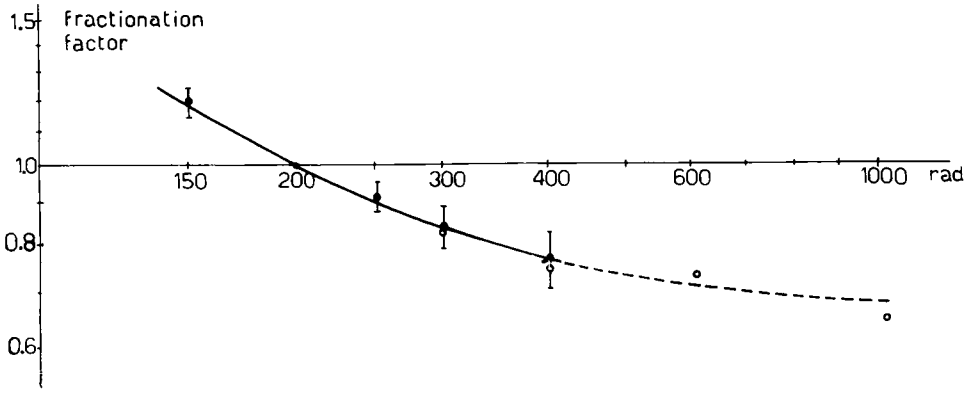

Fig. 1. Fractionation factor plotted against the dose per fraction (reference fractionation 200 rad per fraction 5 days/week). Closed circles indicate the value of the fractionation factor for florid erythema with open circles as late reactions.

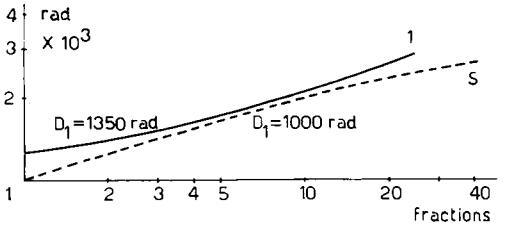

Fig. 2. Florid erythema dose plotted against the fraction number. Curve 1: Present results (15 MeV electron on 4 cm × 12 cm area). Curve S: Strandqvist's erythema curve.

FOWLER & STERN have suggested that no such curve obtained in the clinical field may be explained by survival curves having values of D_0 and n like those appearing in radiobiologic research. The curve obtained in the present series of experiments is however in good agreement with the theoretic curve b; moreover, this curve was obtained with a D_1 of 1 500 rad, almost equal to the experimental value of D_1.

The different time interval between fractions when 400, 600, 1 000 rad per fraction were given make it likely that the value of D_1 obtained in the experiments was higher than the true value because of the intervening recovery phenomena. If D_1 were lower, the curve would considerably steepen, and so would approximate curve b even more closely owing to the high values of the abscissa.

It is suggested that the good agreement between the experimental data and the theoretic curve is due to the substitution in the clinical field of the relationship dose against the number of fractions for the relationship of dose against time. Furthermore it may be caused by the removal through direct comparison of two adjoining sides of the same patient of the errors resulting from a comparison of patients of different sensitivity. Of course, the errors inherent in investigations in

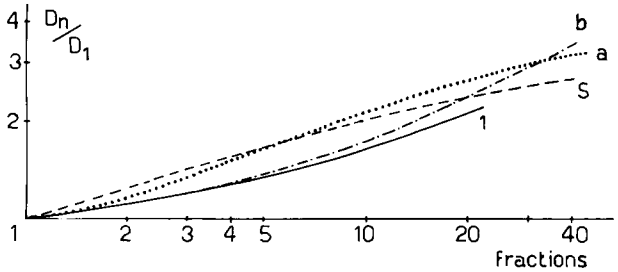

Fig. 3. Ratio D_n/D_1 plotted against the fraction number for present results, for Strandqvist's erythema curve and for certain theoretic curves as follows. Curve 1: Erythema curve, present results (15 MeV electrons, 4 cm × 12 cm area). Curve S: Strandqvist's erythema curve (from FOWLER & STERN). Curve a: Theoretic curve deduced from a survival with $D_0 = 130$ rad, $n = 2.8$, considering $D_1 = 1\,500$ rad (from FOWLER & STERN).

human subjects may raise some doubts about the conclusion drawn, especially when the changes in the values considered are not particularly high.

It may be concluded that the method allows a strict evaluation of the different types of fractionation schedules with the dose values most commonly employed in clinical radiation therapy (150, 200, 300 rad every 24 hours). On the other hand, for doses of 400, 600, 1 000 rad, for which the time between fractions had been increased, a different influence of recovery factors was probably present. Although it would appear that the results obtained are reasonably reliable, even for higher dose values, it must be recognised that the influence of recovery factors has still been insufficiently evaluated. This problem therefore requires further consideration.

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SUMMARY

The authors have evaluated several types of dose fractionation in patients treated after amputation of the breast for carcinoma and irradiated with 15 MeV electron beams to bilateral parasternal lymph nodes. Reactions observed in the same patient with different types of fractionation are plotted and the resulting curves compared with results reported by other workers.

ZUSAMMENFASSUNG

Die Verfasser haben verschiedene Typen von Dosis-Fraktionierung bei Patienten, bei denen nach Amputation der Brust wegen eines Karzinoms bilateral die parasternalen Lymphknoten mit 15 MeV Elektronenstrahlen bestrahlt waren, beurteilt. Rie Reaktionen, die beim selben Patienten mit verschiedenen Typen der Dosis-Fraktionierung beobachtet wurden, werden graphisch dargestellt und die erhaltenen Kurven mit den von anderen Untersuchern beschriebenen Resultaten verglichen.

RÉSUMÉ

Les auteurs ont étudié différents types de fractionnement de la dose chez des malades traitées après amputation du sein pour cancer et irradiées par des faisceaux d'électrons de 15 MeV sur les ganglions lymphatiques parasternaux des deux côtés. Les réactions observées chez la même malade avec les différents types de fractionnement sont mises en graphique et les courbes résultantes sont comparées avec les résultats présentés par d'autres auteurs.

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