

https://dspace.org/

Physical and biological parameters affecting the reaction of human tissues and tumours to ionizing radiation: a statistical and experimental study of the development of methods for determining therapeutic ratios, optimal dosage factors, and a theoretical prognosis in clinical radiation therapy

2015-02-09
http://hdl.handle.net/10539/16953

Downloaded from a DSpace repository. https://dspace.org/

cord (* 27), kidney (* 109), and lungs (* 191). For the purposes of clinical radiotherapy, it is probably safe to assume, in the absence of evidence to the contrary, that these tissues as well as the mucous membranes or other tissues constituting the tumour bed, resemble skin in respect of this factor, thus taking the diffusion constant $q = 0.33$ in all cases.

With malignant tumours, on the other hand, the field-size effect certainly does not follow the same trend as in the case of skin or other normal tissues. The sensitivity of a tumour to radiation is not increased with larger fields, but on the contrary, larger tumours, necessitating larger fields tend, if anything, to be rather more resistant to irradiation. There is some experimental evidence to support this view. However, an attempt to estimate the effect of field-size on human squamous carcinoma considered apart from the surrounding tissues (* 39), showed no consistent trend, the exponent averaging around $q = \pm 0.1$. In the absence of quantitative evidence of any definite trend in either direction, the best available estimate for the diffusion parameter must be taken to be $q = 0$ for all tumours.

THE COMPOSITE ISO-EFFECT FORMULA.

Formula (1, 01) given on page 19 can, in the light of the foregoing analysis, be re-written in a more definite form taking into account all available information on the magnitudes of the relevant parameters for tissues and tumours under all possible combinations of technical factors and other conditions of treatment. The equation may then be specifically formulated as

$$D = E.T^{n}.L^{-q}/\eta \qquad (2, 15)$$

Where the physical dose (D) is the dependent variate, determined by all the other factors. The over-all time (T), the field-diameter (L), and the relative biological efficiency (η), are all independent variates, which can be selected more or less at will by the prescribing radiotherapist. The standard radio-sensitivity (E) and the 'recovery' and 'diffusion' exponents (n and q respectively) are the parameters or statistical constants characteristic of the tissues irradiated. In this way, the dose required to produce any chosen reaction can be

calculated for any given treatment conditions.

The formula is, of course, applicable only to a given single tissue; it cannot, in this simple form, account for the over-all effects resulting from interactions between two or more tissues reacting simultaneously. In clinical radiotherapy, it is precisely such a complex interaction between the tumour and one or more normal tissues which determines the success or failure of a given irradiation procedure. In the following chapter we shall develop the statistical principles underlying the iso-effect formulae, taking into account the two sets of variables and parameters simultaneously, with the object of calculating that tumour dose, which, in any given combination of circumstances, gives the greatest probability of uncomplicated cure.

SUMMARY OF CHAPTER V

The field-size factor, or the effect of varying the size and shape of the irradiated volume upon the intensity of the reaction, is analysed. Appropriate parameters for a variety of anatomical and geometrical configurations are estimated. The factor 'q' is shown to be about 0.33 for skin and probably zero for tumours. This datum completes the information required to formulate an iso-effect function simultaneously incorporating the relevant variates and parameters, for any combination of technical factors.

The composite iso-effect formula has the form $D = E.T^{n}.L^{-q}/\eta$, individual factors having the values determined in previous chapters, so that the dose required to produce a given reaction, with any combination of technical variables, can be calculated.

THIRD PHASE - DEVELOPMENT OF A NEW METHOD FOR COMPUTING THE OPTIMAL DOSE, THE THERAPEUTIC RATIO AND THE PROGNOSIS.

CHAPTER VI. ALGEBRAIC METHODS.

GENERAL VALIDITY OF THE ISO-EFFECT FORMULAE.

As shown in the foregoing chapters, the empirical iso-effect formulae have fairly wide applicability, within the limits of observational accuracy, in clinical radiotherapy. It need not, however, follow that the formulae reflect any underlying principle, nor can one assume the existence of any general regularity or fundamental law which might explain the observed results. In the following paragraphs, the theoretical foundations of the 'recovery' and 'diffusion' processes will be examined more rigorously, with the object of defining the validity of the procedures used, determining the reliability of the estimated parameters, and developing the underlying statistical principles to the point where the optimal tumour dose and its associated prognosis can be computed.

Many different hypotheses have been proposed at various times to account for the dependence-on-time of radiation reactions, or the apparent recovery of the exposed organisms during protracted irradiation. These include physical considerations, exemplified by 'multihit' and 'multi-target' hypothesis (* 113, 105); a chemical factor, attributed to the removal or inactivation of some or all of the chemical radicals or other intermediary products of irradiated protoplasm (* 90); and lastly biological reparative reactions, or 'pseudo-recovery' due to replacement of damaged tissue by proliferation of surviving cells (* 54).

In some studies, notably on the effects of total body irradiation (* 19, 128, 178), the concept of a chemical substance, undergoing simple exponential decay with time, seemed to furnish an adequate description of the experimental data (* 142). This simple concept

concept obviously did not hold in the case of local reactions to large doses; and rather more complex hypotheses have been proposed to account for observed results with the various fractionation schemes used in clinical radiation therapy (* 147, 159, 185).

There is considerable evidence (* 43) from many experiments in the field of radiation biology, for the generation in irradiated tissue of a 'substance' shown to be mobile, locally diffusable, and unstable with a tendency to decay as a function of time. Of these three attributes, the first accounts for the experimental findings in relation to systemic radiosensitizing effects (* 38), and the latter two promise to throw light on the mechanisms underlying the time and volume parameters respectively, as they effect dosage in clinical radiotherapy. The diffusion effect has been observed in irradiated human tissue by the increased radiosensitivity of skin adjacent to another treated area (* 97). The ratio of the treated volume to the bounding surface limits the rate at which the diffusable agent leaves the irradiated region, hence the dependence of the intensity of the reaction upon the size and shape of the treated field. Similarly, loss of the activated material through decay processes amounts to partial recovery of the tissues from the effects of radiation.

It would seem to be a reasonable assumption that the time-dependence of radiation effects results from exponential decay of one or more activated substances in the irradiated region. The extent to which this hypothesis could be made to fit observed clinical data on the effects of fractionation will now be considered.

A 'SINGLE EXPONENTIAL' HYPOTHESIS.

Let us assume, as a first approximation, that radiation generates in tissues a single substance which decays exponentially at a constant rate, and that this substance must reach a particular critical concentration in order to produce a given observed result. Assume that 'E'

is the 'single short exposure' reaching a particular reaction level, and d_1, d_2, ... d_T, are equal daily fractional doses whose sum totals 'D', so that $d_1 = d_2 = \ldots = d_T = D/T$, where T is the number of daily fractions. Each fraction 'd' decays exponentially with time according to the expression $d_t = d \cdot e^{-\lambda t}$, λ being constant for the substance concerned, and 't' the elapsed time in days. If daily fractionated treatment is continued until the required level is reached, that is, when the residual dose $\sum d_t$ reaches the critical level E, then

$$E = \frac{D}{T}\left(1 + e^{-\lambda} + e^{-2\lambda} + \cdots + e^{-\lambda(T-1)}\right)$$

and

$$\frac{D}{E} = \frac{T}{\sum_{x=0}^{T-1}\left(e^{-\lambda x}\right)} \qquad (3, 16)$$

which, since the divisor is the sum of a geometric series, and

$$\sum_{x=0}^{l}\left(a^x\right) = \frac{a^{l+1} - 1}{a - 1}$$

reduces the formula to:

$$\frac{D}{E} = \frac{T(z-1)}{z^T - 1} \qquad (3, 17)$$

where

$$z = e^{-\lambda}$$

The factor 'z' would, with a single decaying substance, be constant, and hence a parameter characteristic of the tissue irradiated.

The problem then devolves upon the following question: Is it possible to choose a value for the parameter 'z' so that the time-factor correction, in this instance the ratio D/E, fits observed data? Cumulative dosage curves based on the above formula (3, 17) are shown by the thin solid lines in Figs. 13 and 14, with 'z' chosen so that the curve intersects data for human skin (Fig. 13) and epidermoid cancer (Fig. 14) at the well-established 30-day factor.

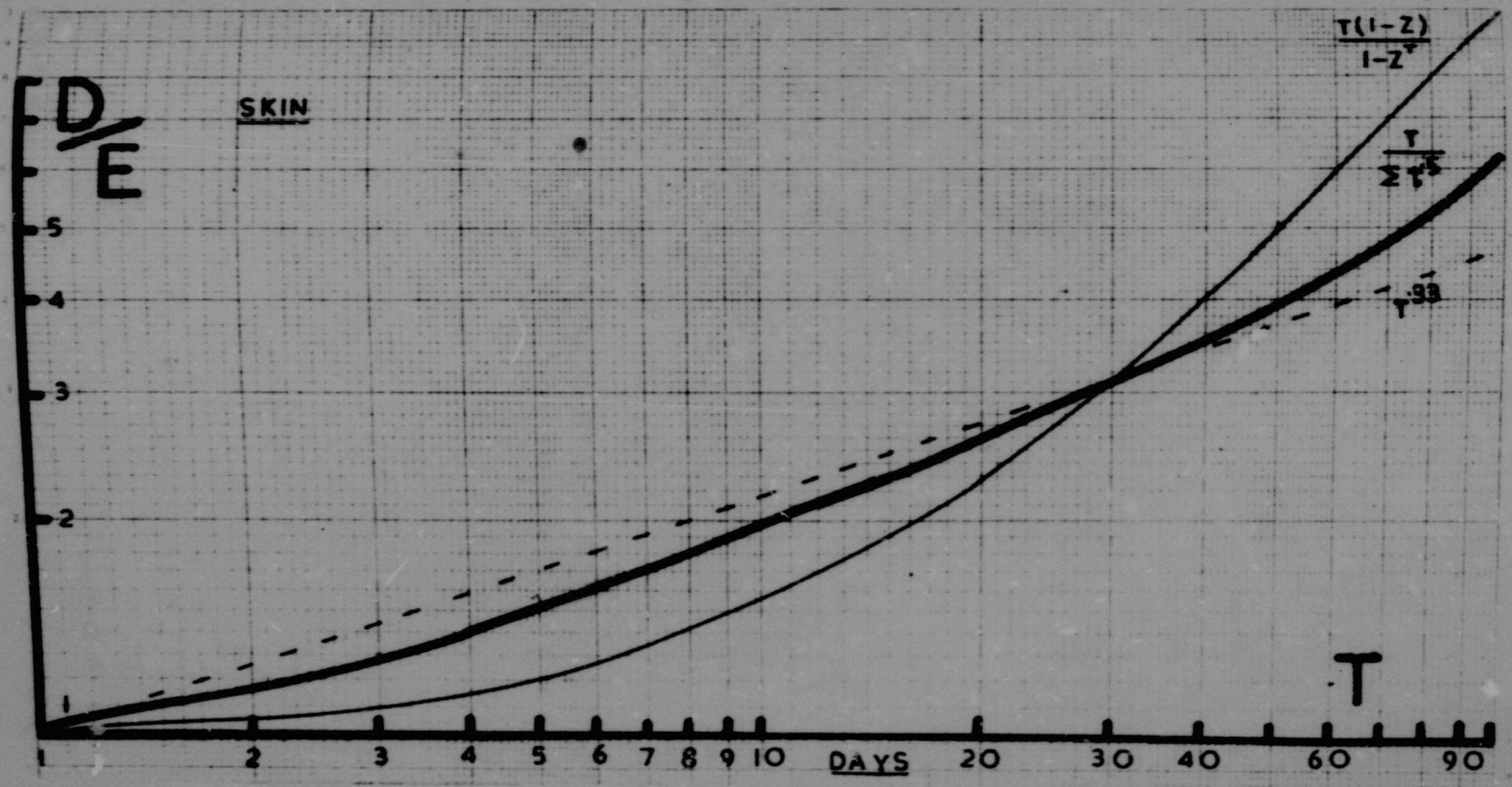

Fig. 13. Comparison of the "single exponential" (thin line) and "mixed exponential" (heavy line) hypotheses in relation to SKIN recovery parameters. The superiority of the latter hypothesis as seen by comparison with the dotted line, representing the slope shown in Fig. 7, based on observed data.

It is obvious from both graphs that this type of curve cannot describe the facts adequately, no matter what z-value is selected. It must be concluded that the hypothesis of a single exponentially decaying substance in irradiated tissues is untenable.

A 'MIXED EXPONENTIAL' HYPOTHESIS.

As an alternative to the hypothesis of a single exponentially decaying substance, one might consider the position with a large number of such products, each diminishing exponentially, but having a wide range of individual decay rates. In view of the heterogeneous mixture of substances constituting the irradiated tissues, the latter alternative would a priori seem by far the more comprehensive description of a necessarily complex situation. It has been shown (* 136) that with such heterogeneous mixtures of exponentially decaying products, the total residual activity (R_t) after a period (t), given by the sum of the exponentials, approximates a power function, that is

$$R_t = \sum_{i=1}^{n} \alpha_i e^{-\beta_i t} \simeq A t^{-g} \qquad (3, 18)$$

where α and β are characteristic of the individual products generated, and 'g' is a constant fraction of negative sign. This function appears frequently both in biological decay systems (* 136) and in physical mixtures such as the radioactive products of a nuclear fission burst (* 190).

Assume, as in the previous example, that E is the instantaneous exposure giving a particular reaction level and d_1, d_2, ... d_T, are equal daily fractional doses whose sum is D, so that $\overline{d} = D/T$, T being the number of daily fractions. Each dose 'd', however, decays with time according to the power law (3, 18), so that $d_t = d.t^{-g}$, t being the elapsed time in days. When $\sum d_t$ reaches the critical level equivalent to E, then

$$E = \frac{D}{T}\left(1 + 2^{-g} + 3^{-g} + \ldots + T^{-g}\right)$$

and

$$\frac{D}{E} = T \Big/ \sum_{x=1}^{T} (x^{-g}) \qquad (3, 19)$$

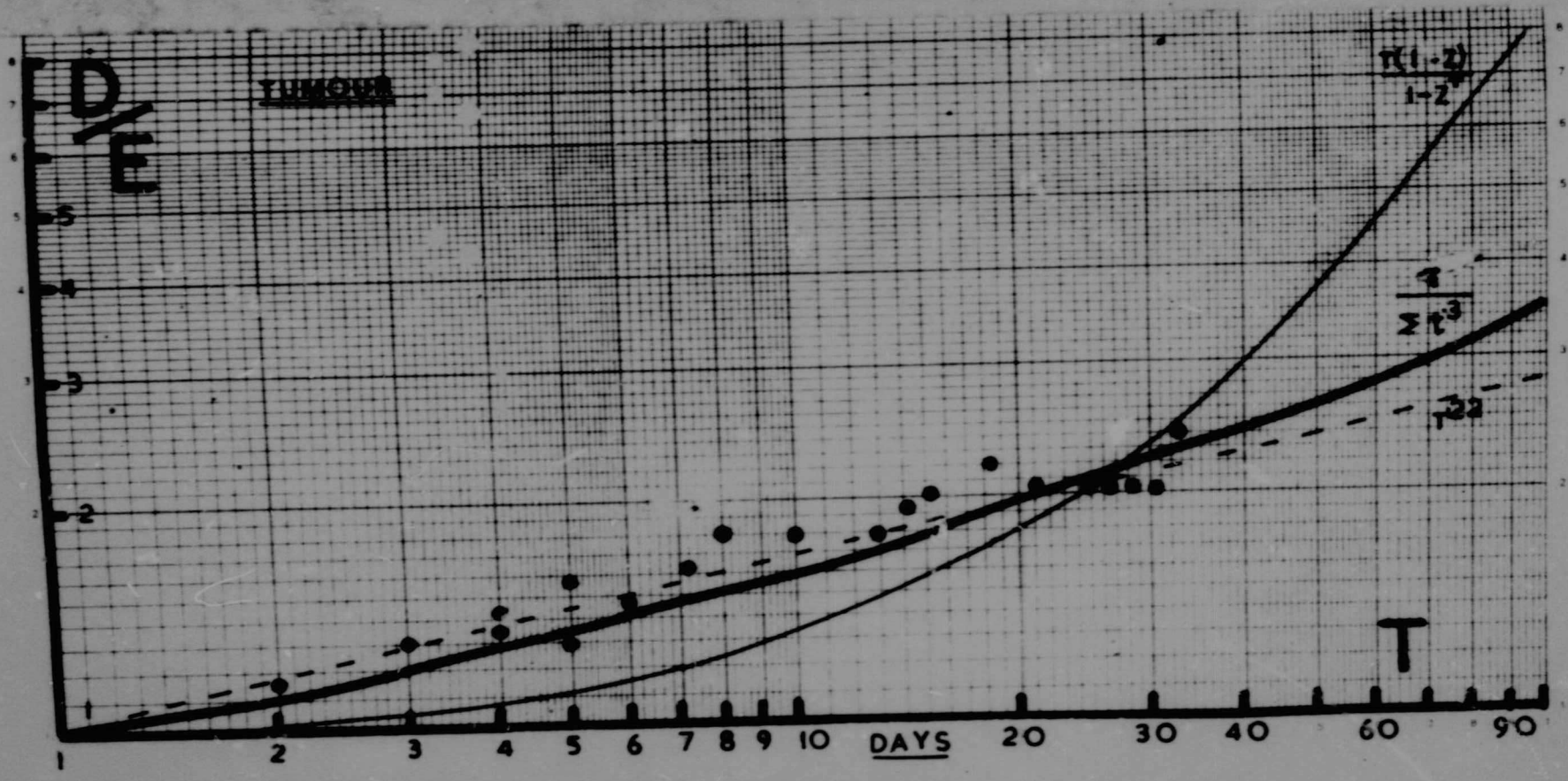

Fig. 14. A similar comparison based on TUMOUR recovery data from Fig. 7. The agreement between the mixed exponential hypothesis (heavy line) and the observational data is obviously far closer than the alternative (thin line).

Choosing a suitable value for 'g' on the same basis as in the previous example, the corresponding curves fitted to the clinical data (heavy lines in Fig. 13 and 14) show a remarkably close correspondence between theory and observation. With g-values of 0.5 and 0.3, a fairly precise description of the time-dose relationships of human skin and squamous cancer respectively is obtained.

The theory of a mixture of unstable and diffusable products of irradiation in tissue would seem to accord, at least within the limits of observational error, with all available clinical and experimental data. The formula (3, 19) may, therefore, be accepted as a satisfactory working hypothesis.

While the formula (3, 19) would seem to furnish a reasonably well-founded mathematical explanation for the recovery function of irradiated tissues and tumours, it is cumbersome by comparison with the simple empirical power functions described in the preceding sections. Within the ordinarily used treatment times, however, say between 1 and 60 daily fractions, there is hardly any difference between the two functions (Fig. 13 and 14). Only with rather extreme fractionation around 100 days or more, is there a considerable divergence between the curves, that derived from the 'mixed exponential' hypothesis indicating a greater recovery at this period than the empirical power function. There are insufficient data to determine precisely which of the two functions fits the facts better, but a few isolated observations on extremely prolonged treatment times, particularly in the case of permanent implants with long-lived isotopes, showed unexpectedly feeble skin reactions even with high dosage (* 42), thus favouring the former hypothesis. This view is confirmed by evidence of a failure to cure epidermoid cancer when the Standqvist plot (see Fig. 7) is extrapolated to 10 weeks or more (8000 r in 70 days is sublethal according to Paterson (* 137).

The validity of this hypothesis is questionable, however, when different fractionation schemes are to be analysed or compared, particularly if unequal or unequally spaced fractions are used. It could be shown, by the same reasoning as in the preceding formulae, that with S fractions delivered over T days, the ratio

$$\frac{D}{E} = \frac{S^{1-g}}{T^{-g} \sum_{x=1}^{s} (x^{-g})} \qquad (3, 20)$$

The parameter 'g' in this expression presupposes a constant shape for the hypothetical 'decay' curve. This is not compatible with observation, as the data upon which the initial recovery curves shown in Fig. 6 are based provide strong evidence for considerable variation in this factor. This suggests that the 'mixed exponential hypothesis', though readily fitted to observed data, is still an over-simplification.

It thus appears that the empirical power-function or iso-effect curve, though lacking any obvious theoretical foundation, is perfectly adequate for continuous or daily fractionated irradiation over ordinary treatment periods. This curve should, presumably, not be extrapolated beyond specified limits, in which cases the alternative 'mixed exponential' hypothesis is preferred.

ESTIMATION OF SKIN RECOVERY AND DIFFUSION PARAMETERS.

The use of algebraic 'regression equations' permits a more rigorous examination of the data analysed in the preceding chapters by graphical methods. Since the iso-effect formulae used are very close approximations to the theoretical recovery and diffusion functions, such algebraic methods would also enable one to estimate parameters, and hence optimal dosage factors, with a known degree of confidence. Implicit in the use of these iso-effect formulae is the assumption that

the recovery and diffusion exponents 'n' and 'q' are independent of the quality of the radiation, and that no allowance need be made for variation among individual patients. It becomes necessary, therefore, to determine the extent to which 'n' and 'q' may be influenced by varying the quality of the radiation; and to estimate, as far as possible, the magnitude of the individual variability.

The tumour dosage data, moreover, were obtained from observations on treated cases published by several authors, among whom the estimated curative dose, and the proportion of cures obtained with this dose, differed very widely. The analysis of these data, therefore, gave rather crude average values, from which more or less deviation is to be expected in individual cases. In order to determine the dose required to cure the growth in all or most treated cases, one has to estimate an additional parameter, namely the 'variance' of the dosage.

For this purpose, evaluation of the response to radiation in a series of radiotherapy cases (* 44) was carried out as follows;. The reactions resulting from treatment with the following six different qualities of radiation was observed;

(a) Radium γ-rays; $\frac{1}{2}$ mm. Pt filtration.
(b) 220 kVp x-rays; 1 mm. Cu filter; HVL 1.5 mm. Cu.
(c) 180 kV (cp) x-rays; $\frac{1}{2}$ mm. Cu filter; HVL 0.9 mm. Cu.
(d) 140 kVp x-rays; $\frac{1}{4}$ mm. Cu filter; HVL 0.4 mm. Cu.
(e) 140 kVp x-rays; 2 mm. Al filter; HVL 0.2 mm. Cu.
(f) 60 kV Chaoul unit; HVL 0.16 mm. Cu.

A total of 150 consecutive cases (25 in each qualitative group), in which the skin dose could be accurately computed were selected for analysis. In order to eliminate uncertainties due to exit doses and the effect of contiguous fields, only those cases treated by a single field were used. In each case note was taken of the skin dose received

(D), the over-all time (T), the field diameter (L), and an estimate of the biological dose (E). D was taken as the maximum surface dose at the centres of the treated field; T is the total treatment time in days irrespective of the manner of fractionation, though in the majority of cases treatment was daily for five days a week; L, in the case of square or circular fields, is the diameter in decimetres, while with irregular fields the equivalent diameter of a circle having the same ratio of area: perimeter is taken, so that $L = \frac{4 \times \text{area}}{\text{Perimeter}}$;

and E could be estimated with a fair degree of precision from the intensity of the observed skin erythema.

Early experiments had shown a rough correlation between the dose delivered and the observed reaction. It had been noted by Sievert in 1947 (* 164) that if the threshold erythema dose (1° E) were determined, then delivery of twice this dose produced a dry desquamative reaction (2° E), three times this quantity gave a moist epidermatitis (3° E), and four erythema doses caused necrosis. In our series of cases the reactions were classified in these four categories, and further subdivided into weak, medium or strong reactions in each major category, thus giving 12 distinct gradations of response. It was considered that the four degrees of reaction correspond to a biological dosage parameter of E = 1000, 2000, 3000 and 4000 respectively, and the intermediate gradations were evaluated by subtracting 300 for weak and adding 300 for strong reactions in each category. For example, a strong dry desquamative reaction would be classified as E = 2300. In this way a quantitative value can be assigned to any observed intensity of skin erythema in steps equivalent to 300 rad single exposure. Although subjective judgment must enter into this type of assessment, the error is unlikely to be greater than one step, that is about 30 per cent for first-degree reactions, and less than 10 per cent for the more intense reactions.

The dose which would produce a standard erythema in each case, under the conditions of treatment, is given by the ratio of the physical dose (D) to the observed biological dose (E). According to our formula, this ratio, designated (R) in Table VII should, within the limits of error and variation, equal a. $T^n.L^{-q}$. It then becomes possible to estimate a, n and q simultaneously by fitting the data, grouped according to quality, to the line

$$\log R = \log a + n \log T - q \log L \qquad (3, 2\text{\$})$$

by the method of least squares.

The procedure used in computing these factors is illustrated in Table VII . (For practical reasons only one section of the complete table is reproduced).

The same procedure was applied to each of the six qualitative groups, estimating in each case the values of a, n and q, and their confidence limits. Preliminary results showed that whereas 'a' varied considerably from one quality to another, showing a definite decrease with diminishing half-value layer, n and q appeared to range about 0.3 without any special trend related to quality, and within each group n and q were sufficiently close, well within the limits of observational error, to warrant the assumption that for practical purposes n = q.

The postulate that n = q simplifies the iso-effect formula to

$$\frac{D}{E} = a\left(\frac{T}{L}\right)^n \qquad (3, 22)$$

which has many important implications. Firstly it lends theoretical support to the phypothesis of a 'diffusible substance (* 77, 97), for diminishing the treated field by a given factor, or increasing the time interval by the same factor, would allow the same proportion of the 'substance' to diffuse accross the surface bounding the treated volume.

TABLE VII

PART OF THE TABULATED DATA FOR REGRESSION ANALYSIS OF SKIN REACTIONS

(Given $D = E.a.T^{n}.L^{-q}$; and $\log R = \log a + n \log T - q \log L$)

140 kV x-rays, HVL 0·2 mm. Cu.

(D) roent.	(E) reactn.	(R) D ÷ E.	(T) day.	(L) dm.	log R	log T.	log L.	log R × log T.	(log T).²	log L × log T.	(log L).²	log R × log L.	Log R (est) Regression values.	Δ.	Δ².
1500	1300	1·15	1	0·1	0·0607	0·0000	−1·0000						0·073	0·012	0·0001
2500	2000	1·25	1	0·1	0·0969	0·0000	−1·0000						0·073	0·024	0·0006
2500	2700	0·93	1	0·15	−·0315	0·0000	−0·8239						0·015	0·047	0·0022
...	...	...	...	...	...	...	...						...	...	...
...	...	...	...	...	...	...	...						...	...	...
...	...	...	...	...	...	...	...						...	...	...
...	...	...	...	...	...	...	...						...	...	...
6000	3300	1·87	15	0·4	0·2718	1·1761	−0·3979						0·265	0·007	0·0001
4200	3000	1·40	12	0·5	0·1461	1·0792	−0·3010						0·200	0·054	0·0029
1500	1300	1·15	5	0·8	0·0607	0·6990	−0·0969						0·005	0·055	0·0030
1200	1300	0·92	5	1·4	−0·0362	0·6990	0·1461						−0·076	0·040	0·0016
1200	1700	0·71	5	2·0	−·1487	0·6990	0·3010						−0·127	0·022	0·0005
				Σ =	1·7177	13·6391	−11·7326	2·1204	12·5868	−4·8460	8·0065	−1·0903		$\Sigma\Delta^2$ =	0·0491

These values and the summated data shown at the foot of each column were derived by mechanical computation

EQUATIONS : 1·7177 = 25·0000 log a + 13·6391 n − 11·7326 q
2·1204 = 13·6391 log a + 12·5868 n + 4·8460 q
1·0903 = 11·7326 log a + 4·8460 n + 8·0065 q.

Whence least squares regression values for
a = 0·54 ± 0·021
n = 0·33 ± 0·013
q = 0·34 ± 0·011

Standard deviation (log) is $\sqrt{\frac{\Sigma\Delta^2}{21}} = \pm 0·048$
Whence 95 per cent confidence limits for dosage data is ± 1·25.

TABLE VIII

SENSITIVITY AND RECOVERY PARAMETERS FOR SKIN REACTIONS TO RADIATIONS OF VARIOUS QUALITIES

Quality of radiation.	"a"*	"n"*	"q"*	Erythema dose range (95% cases).
Radium ; ½ mm. Pt filter	1·05 (± ·024)	0·28 (± ·034)	1·21	870–1260 r
220 kV ; HVL 1·5 mm. Cu	0·76 (± ·030)	0·29 (± ·028)	1·28	600–960 r
180 kV ; HVL 0·9 mm. Cu	0·66 (± ·020)	0·31 (± ·022)	1·23	540–810 r
140 kV ; HVL 0·4 mm. Cu	0·52 (± ·012)	0·32 (± ·021)	1·21	420–630 r
140 kV ; HVL 0·2 mm. Cu	0·54 (± ·015)	0·33 (± ·024)	1·25	430–680 r
Chaoul ; HVL 0·16 mm. Cu	0·49 (± ·025)	0·35 (± ·047)	1·35	370–560 r

* The limits shown are, in each case, standard errors of the estimated parameters.

Further, being two-dimensional, it is possible to test the formula visually by fitting the observed points graphically to the regression lines, as illustrated in Fig. 15. Finally, estimation by the method of least squares of two parameters rather than three permits a considerably greater precision on our estimates of a and n (Table VIII).

The standard deviation (§) of the logarithm of the dosage estimates can be computed in the usual way. In 95 per cent of cases log R lies within the limits of our estimated value plus or minus 2 s. It follows that the equivalent confidence limits for R are given by its estimated value multiplied or divided by a factor U^2, where U is the antilog of S ($U^2 = 10^{2s}$).

It is proposed in this context to call 'U' the 'standard uncertainty factor', in which case U^2 becomes the '5% uncertainty factor'. The final estimates for the three relevant parameters in each of the six qualitative groups are given in Table VIII.

It will be noted that the six radiation qualities are arranged from above downwards in order of diminishing energy. Inspection of column 'a' representing the mean standard erythema dose in kilorad shows that this dose diminishes (or biological efficacy increases) with diminishing half-value layer. Computation of the significance of the differences between adjacent qualitative groups shows that the difference in the biological efficacy of radium compared to 200 kV roentgen rays is highly significant ($P < 0.001$), and the ratio of the two (1: 0.7 = 1.4) is in excellent agreement with other estimates (see Table II). The difference between the 220 kV and 180 kV ranges is statistically significant ($P = 0.01$), but of minor importance clinically, so that for practical purposes the two high-voltage qualities may be grouped together taking 'a' as 0.7. The difference between 180 kV and 140 kV is again highly significant ($P < 0.001$), while the three groups in the superficial therapy range do not differ significantly from

one another (P = 0.3), so that for clinical purposes they may be grouped about a = 0.5. There are thus three clinically distinct quality factors: 1.0 for radium γ-rays; 0.7 for the 200 kV range; and 0.5 for superficial therapy, corresponding to RBE values of η = 1.0, 1.4 and 2.0 respectively.

The general validity of the three quality factors given above is graphically illustrated by the scatter diagrams and regression lines in Fig. 15.

Values for 'n' range from 0.28 to 0.35 and tend to increase as the energy of the radiation is diminished. The differences between these values, even that between the smallest and greatest of them, are not significant (P = 0.25); but the constant trend through the whole series of five comparisons is probably not fortuitous ($P = 2^{-5} = 0.03$). Although it would be of theoretical interest to confirm this dependence of the time-area factor on the quality of the radiation, it is of little clinical importance, and there is no reason to depart from the convenient figure n = 0.33 originally assigned.

The 5%-uncertainty factor of the dosage estimates (U^2, actually the antilog of twice the standard deviation of log R) ranges from 1.21 to 1.35, corresponding to coefficients of variation between 11% and 16%. This implies that in 95% of all treated cases the reaction is unlikely to differ from expectation by more than about 30%, which, considering our subjective estimates of the reactions, is not unreasonable. There are few published data on the variability of human tissues in their response to radiation with which to compare our estimates. However, Helmke (* 85) accurately measured the minimum erythema doses for 93 cases treated experimentally, and obtained data which approximate closely to a lognormal distribution with a mean of 309 r and a standard deviation of 35 r. This coefficient of variation of 12% implied that U^2 is 1.24, in good agreement with our findings.

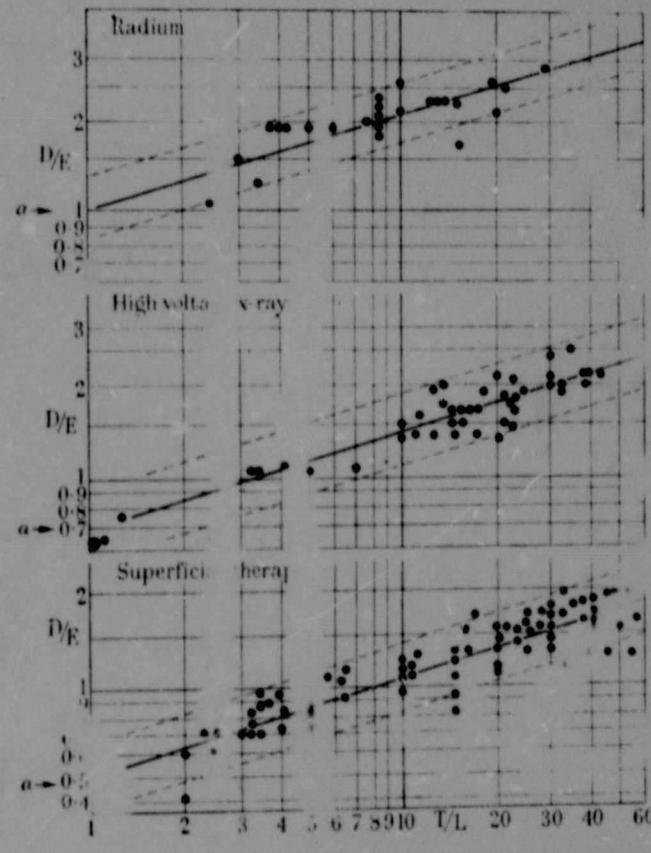

Fig. 15 Scatter diagrams and regression lines illustrating relationship of dose, reaction, time and area for three different qualities of radiation. Broken lines delimit the 95 per cent confidence belt.

DERIVATION OF THE TUMOUR LETHAL DOSE BY 'PROBIT ANALYSIS'.

In the case of tumours treated radically, that is with the object of local 'cure', results are naturally assessed on an all-or-none basis. Each tumour treated results either in 'cure' or 'failure', the probability of cure increasing with dosage according to the usual sigmoid curve. By application of statistical procedures, particularly the method of probit analysis (* 61), the median lethal dose and the coefficient of variation can be estimated directly from the data, and the recovery parameters then computed. In evaluating the curative dosage for epidermoid cancer, these three factors, that is E, n and U for that particular tumour, were derived by the following procedure.

Data from patients with epidermoid cancer in various sites were tabulated and the results analysed statistically. It was necessary to select cases in which not only was the minimum tumour dose known with certainty, but a sufficient follow-up was obtained to enable one to decide whether the lesion had in fact been cured. The records of 100 suitable cases treated between 1946 and 1948, and followed with periodic examinations through 1950, were abstracted and the data collected in Table IX. The cases are arranged in order on increasing biological dosage (E).

The dosage data shown are the true minimum tumour doses, and differed, especially with superficial therapy, from the nominally given doses. In the case of very superficial tumours treated with lightly filtered radiation the significant point was taken to be 5 mm. below the edge of the treated field. With 2 mm. Al filter this point receives about 85 per cent of the given dose; and with the Chaoul apparatus, only 67 per cent. With deeper growths treated at higher voltages, standard depth-dose tables were used to assess the tumour dose; while with radium applicators and implants dosage was calculated on the Paterson-Parker system.

Since various qualities of radiation were used, it was necessary to correct the dosage by a factor (a) which, taking that for γ-rays as unity, becomes 0.5 for superficial therapy, and 0.7 for the 200 kV range (Table VIII). In the case of deep-seated tumours treated with 200 kV radiation, the half-value layer (and hence the RBE) in the tissues differs from that of the incident beam on account of the increase in the average wave-length brought about by the Compton recoil process. This effect is the more marked the harder the incident radiation. From data by Stenstrom and Marvin (* 169) it appears the HVL in the depths approaches 0.7 mm. Cu, irrespective of the quality of the incident ray. This corresponds (Fig. 4) to an RBE of 1.7, whence a = 0.6.

The biological dosage factor E was taken as equal to $\text{Dose}/a.T^n$ where n = 0.25 (as will be explained below a value of 0.25 gave the smallest variance, and is consequently considered the most accurate estimate). The column of results describes the behaviour of the tumours during the three years following irradiation. 'Cured' implies a permanent local regression, irrespective of the patients' general health or the presence of metastases; 'recurred' implies a temporary response of the tumour followed by recurrence within the treated field; where no regression has occurred the tumour is classified as 'persisting'; and in two cases in the higher dosage range the treated area 'necrosed', accompanied by local recurrence.

For the purpose of correlating the probability of cure with dosage, the 100 cases were divided, in order of increasing dosage, into the five equal groups shown in Table IX. The average dose received by each group was determined (on account of some outlying values the median dose was taken in preference to the mean), and the number of cured cases in the group was counted. In Fig. 16a. each step represents one group of 20 cases. The horizontal extent of the step illustrates the range of dosage, while the vertical height indicates the percentage

Since various qualities of radiation were used, it was necessary to correct the dosage by a factor (a) which, taking that for γ-rays as unity, becomes 0.5 for superficial therapy, and 0.7 for the 220 kV range (Table VIII). In the case of deep-seated tumours treated with 200 kV radiation, the half-value layer (and hence the RBE) in the tissues differs from that of the incident beam on account of the increase in the average wave-length brought about by the Compton recoil process. This effect is the more marked the harder the incident radiation. From data by Stenstrom and Marvin (* 169) it appears the HVL in the depths approaches 0.7 mm. Cu, irrespective of the quality of the incident ray. This corresponds (Fig. 4) to an RBE of 1.7, whence a = 0.6.

The biological dosage factor E was taken as equal to $Dose/a.T^n$ where n = 0.25 (as will be explained below a value of 0.25 gave the smallest variance, and is consequently considered the most accurate estimate). The column of results describes the behaviour of the tumours during the three years following irradiation. 'Cured' implies a permanent local regression, irrespective of the patients' general health or the presence of metastases; 'recurred' implies a temporary response of the tumour followed by recurrence within the treated field; where no regression has occurred the tumour is classified as 'persisting'; and in two cases in the higher dosage range the treated area 'necrosed', accompanied by local recurrence.

For the purpose of correlating the probability of cure with dosage, the 100 cases were divided, in order of increasing dosage, into the five equal groups shown in Table IX. The average dose received by each group was determined (on account of some outlying values the median dose was taken in preference to the mean), and the number of cured cases in the group was counted. In Fig. 16a. each step represents one group of 20 cases. The horizontal extent of the step illustrates the range of dosage, while the vertical height indicates the percentage

TABLE IX

RADIOSENSITIVITY AND RECOVERY ANALYSIS OF HUMAN EPIDERMOID CANCER

Case No.	Site.	Field (cm.).	α^*	Dose* (r).	Time (days).	β^*	Result.	Median dose.	Percentage cured.
151	Face	5 ○	0·7	3200	60	1630	Recurred		
152	Orbit	7×7	0·[illegible]	2300	7	1730	,,		
153	Neck node	15×15	0·6	2250	12	2010	Persists		
154	,, ,,	3 ○	0·6	3300	40	2180	,,		
155	Larynx	8×6	0·6	3150	32	2210	,,		
156	Back	3 ○	0·5	2000	10	2250	,,		
157	Tongue	10×8	0·6	3800	45	2430	Recurred		
158	Pharynx	8×6	0·6	3500	23	2650	,,		
159	Neck	10×10	0·5	3000	21	2800	,,		
160	,,	3 ○	0·5	1400	1	2800	Persists	2815	2/20 = 10%
161	Nose	3 ○	0·5	2000	4	2830	Recurred		
162	Alveolus	8 ○	0·5	3000	18	2900	Persists		
163	Neck	8×20	0·5	3150	22	2900	,,		
164	Face	10×10	0·5	3000	18	2980	Recurred		
165	Scalp	14 ○	0·5	3300	26	2980	,,		
166	Larynx	8 ○	0·6	4400	40	2940	Cured		
167	Tongue, base	15×10	0·6	3600	17	2950	Persists		
168	Pharynx	4 ○	1·0	5000	[illegible]	2960	,,		
169	Orbit	7×7	0·6	3750	19	2990	Cured		
170	Face	3 ○	0·5	2250	5	3000	Persists		
171	Temple	4×4	0·5	3300	22	3050	Recurred		
172	Post-cricoid	15×6	0·6	4600	40	3060	Cured		
173	Alveolus	6×6	0·5	3700	33	3090	Recurred		
174	Face	6×6	0·5	3000	14	3100	,,		
175	Penis	8×5	0·7	4200	14	3100	Cured		
176	Scalp	14 ○	0·5	3300	20	3110	Recurred		
177	Epiglottis	10×8	0·6	4600	36	3140	,,		
178	Tonsil	8×6	0·6	4300	26	3140	,,		
179	Face	3 ○	0·5	1600	1	3200	Cured		
180	Larynx	7×7	0·6	4200	23	3200	,,	3200	11/20 = 55%
181	Epiglottis	8×6	0·6	4300	26	3200	,,		
182	Ear, pinna	8 ○	0·5	3350	18	3250	Recurred		
183	Pharynx	15×10	0·6	4000	18	3250	Cured		
184	Nasopharynx	18×10	0·6	4000	18	3250	,,		
185	Nose	4×4	0·7	5000	23	3250	,,		
186	Ear, pinna	2 ○	0·5	2150	3	3260	,,		
187	Scalp	12×12	0·5	3[illegible]	20	3270	,,		
188	Lip	5 ○	0·5	3[illegible]	28	3300	Recurred		
189	Tonsil	10×10	0·6	4100	18	3300	,,		
190	Ear, pinna	2×2	1·0	3300	1	3300	Cured		
191	Lip	8×6	0·5	3600	22	3330	Recurred		
192	Scalp	2 ○	0·5	2000	2	3350	Cured		
193	Face	2 ○	0·5	2000	2	3350	,,		
194	,,	4 ○	0·5	2550	5	3400	,,		
195	,,	3 ○	0·5	1700	1	3400	,,		
196	,,	3 ○	0·5	1700	1	3400	,,		
197	Larynx	8×6	0·6	4500	23	3420	,,		
198	Cheek, oral	5 ○	0·5	3300	13	3480	,,		
199	Scalp	10×10	0·5	4000	25	3500	,,		
200	Hand, dorsum	4 ○	0·5	2700	5	3600	,,	3600	17/20 = 85%
201	Face	3 ○	0·5	1800	1	3600	,,		
202	Penis	4×4	0·5	3400	13	3600	,,		
203	Scalp	3 ○	0·5	3400	12	3620	,,		
204	Lip	7×7	0·7	3650	4	3630	Recurred		
205	Tongue	7×7	0·6	4600	20	3630	Cured		
206	,,	7×7	1·0	7700	20	3640	,,		
207	,,	16×16	0·6	4800	23	3650	Recurred		
208	Neck nodes	18×10	0·6	4500	18	3650	Cured		
209	Nose	3 ○	0·5	3[illegible]50	11	3700	,,		
210	Hand, dorsum	6×	0·5	[illegible]80	[illegible]	3[illegible]	,,		
211	Neck	3 ○	0·5	3700	15	3750	Cured		
212	Lip	4 ○	0·5	3500	12	3760	,,		
213	,,	4 ○	0·5	3500	12	3760	,,		
214	Nose	4 ○	0·5	4000	20	3800	,,		
215	Ear, back	5 ○	0·5	3400	10	3810	,,		
216	Nose	3 ○	0·5	3000	6	3840	,,		
217	Face	3 ○	0·5	2550	3	3850	,,		
218	Branchial	10×8	0·6	4500	13	3950	,,		
219	Alveolus	7×7	0·6	5000	20	2980	,,		
220	Ear, pinna	4×3	1·0	4000	1	4000	,,	4000	19/20 = 95%
221	Hand, dorsum	4 ○	1·0	6000	5	4000	,,		
222	Face	3 ○	0·5	2000	1	4000	,,		
223	Tongue, base	7×7	0·6	5600	29	4000	Recurred		
224	Lip	4×4	0·6	4500	12	4050	Cured		
225	Neck node	6×6	1·0	6400	6	4100	,,		
226	,, ,,	7×7	1·0	6500	6	4150	,,		
227	Nose	3 ○	0·5	4000	13	4200	,,		
228	Ear, pinna	2 ○	0·5	2100	1	4200	,,		
229	Hand, dorsum	4×4	0·5	4500	17	4300	,,		
230	Tongue	5×5	1·0	7000	7	4300	,,		
231	Lip	4 ○	0·5	4000	21	4300	Cured		
232	Ear, pinna	5×2	0·5	4100	13	4300	,,		
233	Face	3 ○	0·5	3400	5	4500	,,		
234	Lip	5 ○	0·5	4200	12	4510	,,		
235	Larynx	4×4	0·6	9500	144	4550	,,		
236	Hand, dorsum	8 ○	0·5	5000	23	4600	Necrosed		
237	Neck	3 ○	0·5	4000	9	4600	Cured		
238	Face	5 ○	0·5	4250	11	4700	,,		
239	Antrum	6 ○	1·0	8000	8	4750	,,		
240	Ear, pinna	8 ○	0·5	5200	21	4850	Necrosed	4850	17/20 = 85%
241	Temple	3 ○	0·5	4200	9	4850	Recurred		
242	Face	3 ○	0·5	3800	5	5000	Cured		
243	Cheek	2 ○	0·5	2500	1	5000	,,		
244	Face	3×2	1·0	6700	2	5050	,,		
245	Cheek	4×4	0·5	5200	15	5200	,,		
246	Face	3 ○	0·5	5100	13	5310	,,		
247	Nose	3 ○	0·5	6000	16	6000	,,		
248	Scalp	8 ○	0·5	6000	16	6000	,,		
249	Forehead	3 ○	0·5	6000	14	6200	,,		
250	Face	2×2	0·5	5100	7	6200	,,		

Author Cohen L
Name of thesis Radiation Parameters 1960

PUBLISHER:
University of the Witwatersrand, Johannesburg
©2013

LEGAL NOTICES:

Copyright Notice: All materials on the University of the Witwatersrand, Johannesburg Library website are protected by South African copyright law and may not be distributed, transmitted, displayed, or otherwise published in any format, without the prior written permission of the copyright owner.

Disclaimer and Terms of Use: Provided that you maintain all copyright and other notices contained therein, you may download material (one machine readable copy and one print copy per page) for your personal and/or educational non-commercial use only.

The University of the Witwatersrand, Johannesburg, is not responsible for any errors or omissions and excludes any and all liability for any errors in or omissions from the information on the Library website.