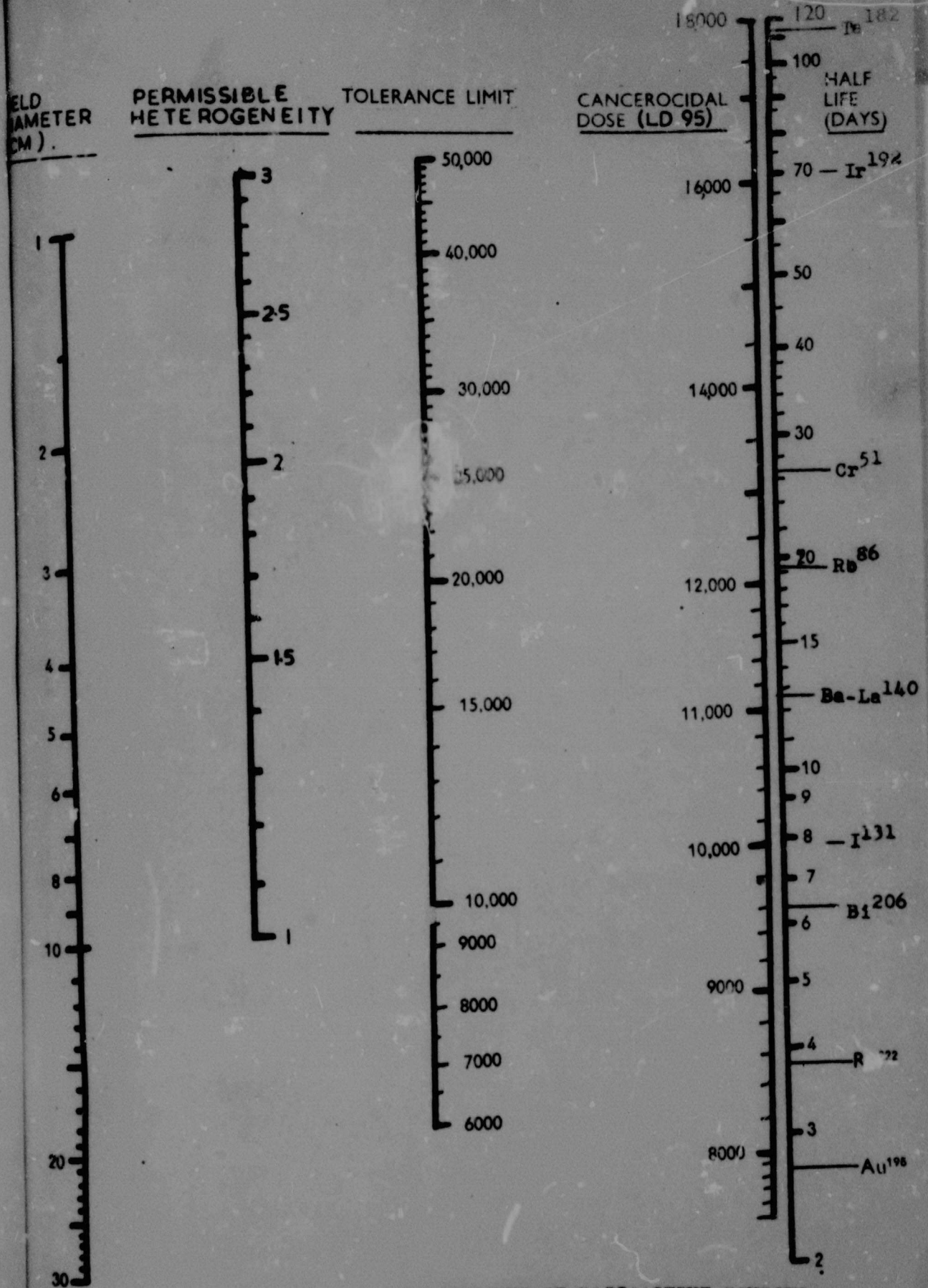


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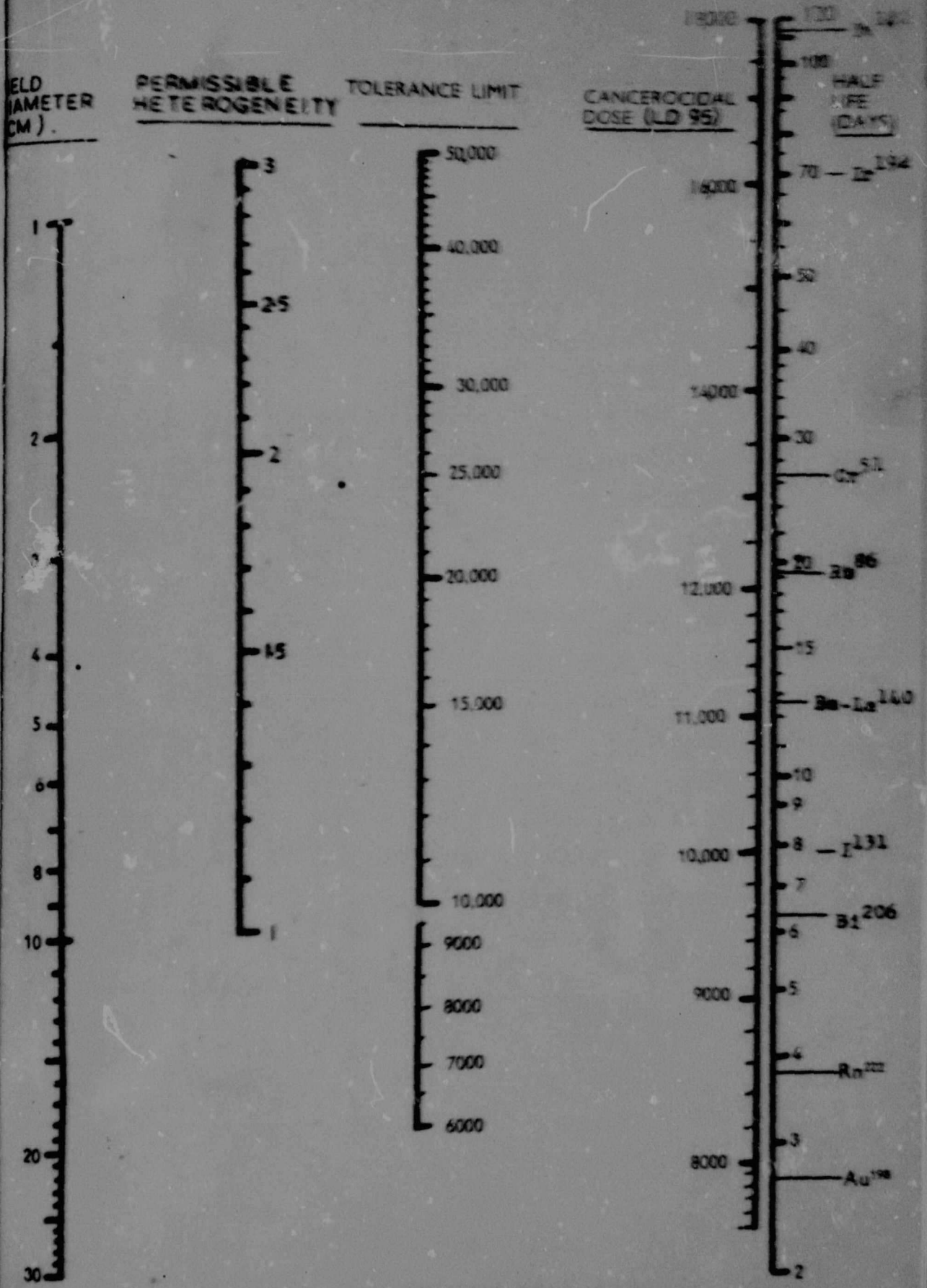
Physical and biological parameters affecting the reaction of human tissues and tumours to ionizing radiation: a statistical and experimental study of the development of methods for determining therapeutic ratios, optimal dosage factors, and a theoretical prognosis in clinical radiation therapy

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DOSAGE NOMOGRAM FOR PERMANENT IMPLANTS OF RADIOACTIVE SOURCES



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It is apparent from the figure that the protracted irradiation obtained with the longer-lived sources such as Ta-182 has, in certain difficult situations, very material advantages over conventionally used materials and procedures.

PRECALCULATED OR INDIVIDUALISED DOSAGE ?

The foregoing analysis on the relation of therapeutic ratio to the statistical prognosis permits one to compare the merits, and perhaps to select, for a given patient, the more appropriate, of the two common radiotherapeutic approaches to the management of curable cancer, through precalculated and individualised dosage schemes respectively. The former approach implies the prescription of an optimal dose derived either from accumulated experience or by calculation, to be delivered regardless of the individual reaction; arguing that any departure from optimal dosage on the basis of an early observed response, would be tantamount to uninformed guessing as to the final outcome, and hence likely to diminish the patient's chance of cure. On the other hand, the 'individualised' school requires that the early response be observed closely during the course of treatment and the final dosage adjusted according to the individual reaction, perhaps reducing the dose in case of unusual sensitivity, thereby avoiding complications, and giving additional treatment should the initial response be milder than expected.

Fundamentally, the difference between these two approaches depends upon whether the 'cure' and 'necrosis' curves are considered stochastically independent or otherwise. If they are, that is if there is no correlation between the curability of the tumour and the observed skin and mucosal reactions, then there is no way of assessing the curability of individual tumours, and individualisation of dosage is to be avoided. Conversely, if the two curves are fully correlated, then these cases showing more marked early reactions and a tendency to necrose at comparatively low doses, will also be cured at correspondingly low doses; in which cases treatment should be wholly individual, aiming at the production of a standard observed reaction in each case.

In practice neither of the alternative postulates can be wholly correct. To get a true picture of the situation would entail measurement of individual radiosensitivities of tumour and skin (possibly adapting the graphical methods devised) in a sufficient number of patients to permit a statistical analysis of the components of variance in both curves. It appears that there must be some <u>independent variation</u> in tumour sensitivity to account for the optimal dosage histograms reported by Tod (* 180), by Paterson (* 139), Garcia (* 8), and Nolan and du Sault (* 135). There must also be a '<u>virtual correlation</u>', in so far as changes in apparent radiosensitivity are attributable to dosimetric fluctuations, which would affect the whole treated area, skin and tumour, simultaneously. There is also some evidence for the existence of a third element, a true <u>individual correlation</u> between the radiosensitivity of tumour and host tissues (* 69, 70, 106).

It must be concluded, therefore, that some individualisation is permissible and perhaps desirable, but only to the extent of a strictly limited deviatich from the precalculated optimum. In the absence of definite statistical estimates of the degree of correlation between the radiosensitivities of skin and tumour, it is safest to assume the major correlated variation to be dosimetric, so that the permissible deviation from the optimum should be little greater than the dosimetric error. Since the accumulated error in total dosage is, in most clinics, of the order of 10%, one might at a guess allow no more than ± 15% individual adjustment. This means that when a course of treatment is long enough to permit evaluation of the reaction intensity before completion, say over 4 weeks, it is permissible to reduce or increase the prescribed dose, according to whether the reaction is more or less severe than the average, by a factor not exceeding 15%.

This conclusion is supported by Friedman's (* 64) clinical experiment on 'single portal, massive dosage' irradiation of certain oropharyngeal tumours. From this it appears that one might prescribe

an 'optimal' skin dose of 6000 rad through a 10 cm portal delivered in equal daily fractions over a period of 4 weeks. During the final week of treatment the average patient (that is at least half of all cases) will show a moderate desquamative reaction, which, it is known from experience, will eventually reach an exudative stage and then heal uneventfully. In some cases it will be distinctly worse than average, and treatment may be curtailed somewhat but not to less than 5000 rad; in others the reaction will be less severe and treatment can be continued to 7000 rad. Since, in the latter instance, the time-factor has been extended to 5 weeks or more, a further increase in dosage becomes possible, and doses up to 8000 rad have been tolerated by a few selected individuals. The cure rate has been shown to be substantially greater when these very high skin doses can be given.

CONCLUSIONS.

The foregoing arguments were more-or-less rigorously based upon statistical considerations, and thus give a fair estimate of the dose of radiation which is optimal in the sense that it permits the greatest probability of uncomplicated cure that can be obtained within the limitations set by the extent and inherent radio-sensitivity of the tumour. Use of the term 'optimal' in this regard is, however, an over-simplification. Implicit in this approach is the assumption that, while uncomplicated cure is desirable, all failures, be they early or late recurrences with or without high-dose effects, necrosis or other complications, are equally undesirable. From the viewpoint of the patient's well-being, it is obviously incorrect to give equal weight to these various sequelae.

Taking an extreme example, consider a low-grade mammary cancer, which, it is known, will not induce any discomfort or complications over a period of many years, in an elderly woman whose normal expectation of life is shorter than the natural history of the tumour. Under these circumstances, low-dosage irradiation, giving temporary remission,

is obviously preferable to the severe reactions with the concomitant risk of high-dosage effects, unavoidably associated with optimal curative doses. In other words, some individualisation, provided it is based upon accurate knowledge of the probabilities operating in each situation, is not without merit in many, if not all cases.

If all the associated biometrical exigencies are to be taken into account, the probability curve for the tumour lethal effect would have to be replaced by a much more complex statistical function, in which the probable duration, as well as the frequency, of tumour regression in relation to dosage is weighed against the grade or expected growth-rate of the recurrent tumour, and also against the expectation of life of the patient as determined by such factors as age, intercurrent disease or other complications. The 'tolerance limit' or 'necrosis risk' functions would become even more complex and would necessarily comprise many imponderable variables such as the psychological, economic, occupational and social implications of a radio-necrotic lesion; its situation, extent and severity, the subject's threshold for pain or other discomfort; the suitability and efficacy of analgesic or rehabilitative medication; and the anatomical extent of the lesion in relation to possible reparative surgery or other procedures designed for symptomatic relief.

The mathematical procedure required to compute the 'quantum of satisfaction' associated with a given treatment in relation to the foregoing statistical and personal considerations, is exceedingly complex and beyond the scope of this thesis. It is probably met, to some extent, by such modern statistical approaches as the 'theory of games' (* 21) the problem being essentially one of a complex strategy with incomplete information. Such problems are well-suited to the capacity of the larger digital computers.

It now seems that a new and radical advance in the radiation therapy of human cancer might become possible. With the introduction of the rad, physical dosimetry has become sufficiently accurate and consistent for true international comparisons, permitting the exchange of data and experience, to be made with confidence. Secondly, the development and wide acceptance of megavoltage generators for therapeutic use, has eliminated all purely physical factors limiting the ability of the prescribing radiotherapist to deliver a desired dose to a tumour in almost any situation. Finally, the biometrical methods developed in this thesis permit one to assess and control the effects of a variety of biological dosage factors, and point the way to the possibility of computing optimal doses and other conditions of treatment.

It is felt that the next logical step should be an international conference, or similar concerted effort, to bring together the combined resources of radiotherapists and biometricians. Its main object would be to exploit the latest advances in computer technology, in order to calculate optimal dosage parameters for all human tumours. When the vast mass of quantitative information on the natural history and response to treatment of all cancer patients has been extracted from hospital records throughout the world and subjected to the appropriate statistical operations, it will no doubt become possible to devise individualised and well-balanced prescriptions for clinical cancer therapy. It may not be too optimistic to expect that this approach would lead to substantially improved cure rates.

SUMMARY OF CHAPTER VII.

Using the mathematical models developed in the previous chapters, the optimal dose (that giving the greatest probability of uncomplicated cure) for a given tumour type treated with any required set of technical variables, is computed. The effect of the time and area factors upon the prognosis is estimated, and the relative advantages of the precalculated and individualised dosage schemes compared. Clinical dosage nomograms, facilitating the practical use of optimal dosage factors in radiotherapy, are constructed. It is concluded that statistical analysis of enough relevant clinical data would permit optimal dosage schemes to be applied to most human tumours, with a corresponding improvement in cancer cure-rates.

* * * * *

DEFINITION OF TERMS

Much of the terminology applied in this work is used in a more limited and exact sense than in the usual clinical context. The analysis also entails the juxtaposition of technical terms from several disciplines - biology, physics and mathematics - in which the same words have distinct meanings. For these reasons, the following list of terms, re-defined in therestricted sense of this thesis, is appended:

BIOLOGICAL DOSAGE: If, with a given set of technical factors, a physical dose of 'D' rads gives the same biological end result as 'E' rads would under standard conditions (a single exposure of high-energy radiation to a 10 cm field), then 'E' is the biological dose corresponding to 'D' rads under the conditions of treatment.

BIOMETRY: Application of mathematical or statistical methods to quantitative biological data.

COEFFICIENT OF VARIATION: The standard deviation (qv) expressed as a percentage of the mean; suited for comparing non-normal distributions around means or medians of varying absolute magnitude.

CURE: Permanent regression (qv), or apparent disappearance of a growth for a specified period, generally 5 years.

CURATIVE or LETHAL DOSE: That quantity of radiation which will result in cure of a specified proportion of cases, usually 50% (LD-50) or 95% (LD-95).

DIFFUSION: See FIELD-SIZE.

DOSE: The amount of energy imparted to matter by ionizing particles per unit mass of irradiated material at the place of interest. It is expressed in rads (qv).

DOSE, ERYTHEMA; THRESHOLD; (TED): A quantal measure of radiosensitivity (qv). The quantity of radiation which will produce a perceptible reddening of the treated area, visible 2 weeks after exposure, in a given proportion of cases (80% after Quimby's method).

DOSE, INTEGRAL: The total amount of energy absorbed in the irradiated organism; the sum of the absorbed doses in each unit mass (or volume) of the organism; expressed in ergs or in gram-rads (= 100 ergs) or in megagramrads (1 M.g.r = 10 joules).

DOSE, OPTIMAL: That particular level of dosage at which the prognosis (qv), or probability of uncomplicated cure, is at a maximum.

DOSE, TOLERANCE: A quantal measure of radiosensitivity (qv). The maximum quantity of radiation permitting healing without permanent structural damage or loss of function.

DOSE-RATE or INTENSITY: Dose per unit time; rads per minute.

ELECTRON-VOLT: The increase in energy or the work done on an electron (or other unit charge) when passing through a potential difference of 1 volt. Energies of particles or of photons are expressed in units one thousand (KeV) or one million (MeV) times greater. A rontgen ray generated at a particular kilovoltage (kV) necessarily carries a numerically smaller quantum of energy (KeV).

ERYTHEMA: See DOSE.

FIELD or FIELD-SIZE: The size of the irradiated region described as the area of an entrance portal or as the total irradiated volume. For biometrical purposes, it is best expressed as the diameter (L) of a symmetrical volume, or as the equivalent diameter of a cube having the same ratio of volume to bounding surface. The effect of field-size on radiosensitivity is shown to be governed by a power law of the type $D = kL^{-q}$, where 'q' is termed the diffusion exponent.

FRACTIONATION: See TIME-FACTOR.

HETEROGENEITY FACTOR: The ratio of maximum tissue dose to minimum tumour dose. In the case of external beam irradiation, it is a reciprocal function of the percentage depth-dose at the tumour.

IONIZATION: Ionizing radiation means electromagnetic or corpuscular

radiation capable of producing ions directly or indirectly in its passage through matter. The number of ionizing events in each micron of path is termed ion-density (ions/μ), or linear energy transfer (LET in KeV/μ), each ion acquiring energy to the value of 0.03 KeV.

ISO-EFFECT FORMULA: A function relating the biological dose 'E' (qv) with the physical dose 'D' (qv), the RBE 'η' (qv), the over-all time 'T' (qv), the field-size 'L' (qv), and the recovery and diffusion parameters 'n' and 'q' respectively, expressed as $D = E.T^{n}.L^{-q}/\eta$.

LINEAR ENERGY TRANSFER: See IONIZATION.

MEDIAN: A statistical measure of average tendency or position; that value of the variate (qv) on each side of which lie equal numbers of observations. A median dose is the ED-50.

NECROSIS: A severe reaction (qv) to ionizing radiation characterised by permanent destruction of tissue or a non-healing defect.

NORMAL DISTRIBUTION or NORMAL CURVE: The distribution of measurements resulting from chance variation of a quantitative magnitude, best described by the Gaussian formula $y = \frac{N}{\sigma\sqrt{2\pi}}\, e^{-\frac{x^2}{2\sigma^2}}$. σ being the standard deviation (qv). With radiosensitivity data the logarithms of doses are generally normally distributed.

PARAMETER: A quantity whose value specifies a population; a statistical or estimated constant.

PROBIT: A scalar transformation; an abscissa corresponding to a given probability in a normal distribution with unit variance. It has the effect of giving a linear regression of probability against dose, or in this context, against log-dose.

PROGNOSIS: The probability of uncomplicated cure (qv) after irradiation of a tumour under given conditions, as assessed by statistical dose-effect functions.

PROTRACTION: See TIME-FACTOR.

QUALITY: A description of the nature, prticularly the energy, of beam of ionising radiation, corresponding in the case of photons, to the average wave-length, quantum energy,

exciting voltage, or the half-value layer in a given absorbing medium. The 'LET' (qv) and 'RBE' (qv) are functions of the quality in this sense.

RAD: Unit of absorbed dose: 100 ergs per gram.

RADIORESISTANT: Descriptive of a tumour which can be cured (qv) only by a dose of radiation exceeding the limits of normal tissue tolerance (qv).

RADIOSENSITIVE: Descriptive of a tumour which responds readily to, or can be cured by, a dose of radiation well below the limits of normal tissue tolerance.

RADIOSENSITIVITY: A measure of the intensity of a biological reaction (qv) to a given dose of radiation (graded response method). Alternatively, described by the quantity of radiation required to produce a reaction of specified intensity (quantal response method).

REACTION: The series of biological changes occurring in tissue as a result of exposure to a sufficient dose of ionising radiation.

RECOVERY: See TIME-FACTOR.

RECURRENCE: A failure to cure (qv). Reappearance of a growth following apparently complete regression (qv).

REGRESSION (...OF TUMOUR): The reaction (qv) in an irradiated tumour leading to a progressive reduction in size and eventual disappearance.

REGRESSION (STATISTICAL): A function relating one dependent variate (qv) to one or more independent variates.

RELATIVE BIOLOGICAL EFFICIENCY (RBE): The ratio between the absorbed dose of high-energy photons and the dose of the radiation in question required to produce the same biological effect in both instances. Taken as 1.00 for radium γ-rays, the RBE is correspondingly greater for radiations of greater ion-density or 'LET'.

RONTGEN or 'r': "The röntgen shall be the quantity of X- or γ-radiation such that the associated corpuscular emission per 0.001293 gm of air produces, in air, ions carrying one electrostatic unit of quantity of electricity of either sign" (I.C.R.U.).

STANDARD DEVIATION (or ERROR): The root-mean-square of deviations about the mean (or median), equal to the square-root of the variance (qv). The standard error of an estimate is the standard deviation of the hypothetical normal population of which the estimate is a sample.

THERAPEUTIC RATIO: A ratio of tissue tolerance (qv) to tumour lethal (qv) doses. A series of therapeutic ratios depending upon acceptable risks of necrosis (qv) and recurrence (qv) may be defined. The ratio of median values is, in this context, termed θ.

TIME FACTOR: Factor by which the physical dose, if delivered at a low intensity (protraction) or if interrupted (fractionation) over a long period, needs to be increased in order to produce the same reaction as a single short exposure. This effect is shown to follow a power law of the type $D = k.T^n$, where 'T' is the over-all time and 'n' the recovery exponent.

UNCERTAINTY FACTOR: A measure of dispersion, variation or error of observations or estimates derived from a log-normal population. Algebraically, it is the antilog of the standard deviation (qv) of log-dose, designated 'U' in this context. Then U^2 is the "5% uncertainty factor".

VARIANCE: A measure of dispersion; average of the squared deviations of observations from their mean or median.

VARIATE: A statistical variable, or quantity whose magnitude can be selected or controlled, as opposed to a parameter (qv) whose magnitude is constant and determined by the nature of the population studied.

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