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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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is the reaction and the greater the risk of necrosis. It often happens in practice (and this will be obvious from the curves in Fig. 1.) that a dose small enough to entail no risk of necrosis has little chance of effecting a cure; and conversely, it may not always be possible to approach a certainty of cure without risking a very high incidence of necrosis. It can be proved that, under such circumstances, there is always a single optimal dose where the probability of uncomplicated cure without necrosis is maximal. The estimation of this optimal dose and development of methods for assuring uncomplicated cures with various types and stages of malignant growth, are the main objectives of clinical radiobiology of cancer.

CLINICAL DOSAGE STANDARDS.

In clinical radiotherapy, the intensities of at least two simultaneous biological reactions have to be considered. One has firstly to assess the response of the tumour and, basing one's judgment upon accumulated experience on the radiosensitivity of tumours of the same general type, to choose a tumour dose large enough to destroy the growth. At the same time, it is equally, if not more, important to ensure that the tolerance dose for the surrounding normal structures is not exceeded. If the tissue tolerance is substantially greater than the tumour lethal dose, it would seem logical for the radiotherapist to choose a dose between these two values, thus effecting a cure without complications. In practice, the situation is by no means so simple, as there is considerable individual variation in the response of both tumour and normal tissue. In other words, it is not two fixed quantities one has to compare but two statistical distributions or sigmoid curves each having some measure of central tendency (median effective dose) as well as a certain spread (coefficient of variation). In general, the two curves will overlap more or less according to circumstances. Further, the relative radiosensitivities of tumour and normal tissue will vary according to the technical factors chosen in the treatment procedure.

# TABLE I

ESTIMATES OF THE STANDARD 'RADIOSENSITIVITY PARAMETER' FOR HUMAN SKIN AND TUMOURS

Data applicable to single 'short' exposures through a 10 cm diameter field; figures in the right-hand column may be used for factor 'E' in the iso-effect formula.

| | rad @ 200 kV (100 ions/$\mu$) | rad @ >1 MeV (10 ions/$\mu$) |
|---|---|---|
| Median Erythema Dose, or 'T.E.D.' | 700 | 1000 |
| Median Desquamative, or Clinical 'Tolerance' Dose | 1500 | 2000 |
| Median Exudative Dose, or Maximum Tolerance Limit | 2000 | 3000 |
| Probable Median Necrotising Dose | 2800 | 4000 |
| Epidermoid Cancer LD-50 | 2000 | 2900 |
| Epidermoid Cancer Lethal Dose (LD-90) | 2500 | 3600 |
| Mammary Cancer LD-50 | 1270 | 1800 |
| Mammary Cancer Lethal Dose (LD-90) | 1600 | 2300 |

The quantitative values shown in Table I are parameters, or statistical estimates, of the radiosensitivity of human skin and tumour measured under standard conditions. It will be noted that the median lethal dose for epidermoid cancer (high-voltage roentgen rays, HVL 1 to 3 mm Cu) is 2000 rad. It then follows that 2000 X 1.3 = 2600 rad should cure 98% of cases, and this quantity may confidently be taken as the lethal or cancerocidal dose for this tumour. Similarly, the median doses required to produce other reactions under standard conditions of exposure are tabulated. The fact that, in this Table, the curative dose exceeds the skin tolerance by a large factor simply means that the standard conditions chosen, that is, a single exposure through a 10 cm field, are unsuitable for treating this tumour. In the following chapters, it will be shown that the relative magnitudes of these two doses can be altered or reversed by a different choice of factors.

Each of the reactions tabulated is dependent on a particular quantity of radiation or a specific dosage level. This specification is, in itself, not sufficient, since if a given tissue is subjected to the same physical dose of radiation under various conditions, the result is not identical in all cases. It has been shown that the biological effect depends not only on the number of ions generated in the tissue, but also on the distribution of those ions in space and time, the biological effectiveness of a given physical dose of radiation thus depending upon several technical variables. In practice, the response of most animal tissues, both normal and malignant, is reasonably consistent if the quality of the beam, the over-all time of the irradiation and the size of the treated field are kept constant. While there are many other variables affecting radiosensitivity to some small degree, they are of relatively little importance, so much so that if the dose received by any given type of tissue is specified, and the relative biological effect of each of the above factors either controlled or

allowed for, the response of the tissue to that dose may be predicted. Conversely, if the effects of variation of quality, time and field-size are eliminated by maintaining standard conditions, or alternatively, by introducing appropriate correction factors, it is possible to specify the dose which will produce certain well-defined reactions, and estimate any individual variability in this regard.

BIOLOGICAL DOSAGE AND TECHNICAL VARIABLES.

In clinical radiotherapy, there are found to be six factors which can affect the outcome of treatment significantly. Three of these are technical variables more or less under the control of the prescribing radiotherapist, and, in a strict statistical sense, should be termed 'variates'. These include:

(1) The quality, a term collectively describing such attributes as the half-value layer, equivalent wave-length, quantum energy, specific ion-density, or linear energy transfer, all of which may here be subsumed under the single quality-function termed 'relative biological efficiency' for the radiation used;

(2) The time factor, that is, the over-all duration, measured either in days or in the number of fractions, specifying the interval between fractions, over which the course of treatment is spread; and,

(3) The field-size, that is, the area, volume, or some equivalent measure of extent, of the irradiated block of tissue.

The three other factors cannot be controlled but are determined by the nature of the tissue or tumour irradiated. They are, in a sense, statistical constants, or 'parameters', which include;

(4) The radiosensitivity of the tissue or tumour in question as assessed by the dose required to produce a given response;

(5) The recovery rate of the irradiated tissue or tumour, as determined by the amount the dose has to be increased to compensate for the effect of protraction or fractionation; and,

(6) The diffusion constant for the irradiated volume as estimated from the effect on the reaction of variation in field-size and shape.

The relationship between the physical dose (D) delivered with a particular combination of quality, time and field-size, and the biological sensitivity (E), as assessed by the dose producing a given reaction under certain specified standard conditions, can be expressed empirically as

$$D = E.\ a.\ b.\ c, \qquad (1,01)$$

where a, b, and c are the factors by which the standard dose has to be adjusted to compensate for differences in quality, time and area respectively. If, under a standard set of conditions, a. b. c. = 1, then E = D, and can hence be measured directly. For the purpose of this analysis, it is convenient to take a = 1 when the specific ion-density is minimal (see next section), say around 10 ions/$\mu$, which holds true for $\gamma$-rays and photons with a quantum energy above 1 MeV. Similarly, b = 1 when the time-factor is minimal, as with single 'short' exposures (the meaning of 'short' in this context will be defined later); and c = 1 at an arbitrarily chosen large field-size, a one decimeter diameter circle being a clinically convenient standard.

Having once determined 'E' for a given reaction under the standard conditions, it becomes possible to calculate the dose 'D' giving equivalent results under any other combination of factors, by introducing the appropriate values for a, b, and c in the equation. Fairly accurate estimates of the magnitude of these three factors can be derived, at least for the skin and for epidermoid and mammary cancer, so that absolute tumour lethal doses and tissue tolerances may be specified in these cases and remain valid under all practicable treatment conditions.

(6) The diffusion constant for the irradiated volume as estimated from the effect on the reaction of variation in field-size and shape.

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In the case of most human tissues and tumours other than normal skin, epidermoid cancer, and mammary cancer, it has not been possible to establish median effective doses under the standard conditions described. In practice, the quality, time, area, and dosage factors are usually determined by clinical exigencies, so that comparative radiosensitivities can only be estimated by extrapolation. If a large body of clinical data is available, graphical methods such as plotting the so-called 'time-effect' curves will then meet this requirement with sufficient accuracy.

Empirical knowledge of optimal dosage procedures for clinical purposes, and some of the effects of changing the quality, time and volume factors has accumulated with radiotherapeutic experience throughout the years. Gareia (* 67) and Strandqvist (* 173) first showed in 1943 how such clinical experience could be systematised by plotting the results of dosage against time graphically, and distinguishing on the graph under- and over-dosage responses. Strandqvist's analysis of the time-dose relationship, though neglecting some essential refinements, was the first direct application of this idea.

By using suitable scales moreover, the function can be transformed into a straight line easily fitted by eye, so as to delimit with fair accuracy the optimal dosage range for all treatment times. The 'position' of this line on the dose axis then gives a measure of the absolute radiosensitivity of the tumour, while its 'slope' is indicative of a specific recovery factor.

Strandqvist's graphs indicate a lethal dose for epidermoid cancer of 2250 rad given in a single exposure, increasing with protraction according to a specific power law to be described. Several other analyses of skin, mouth, and genital epidermoid tumours have given the same results. Using a similar indirect graphical method, the $ID_{50}$

for mammary cancer has been estimated to be 1270 rad (* 40) which is compatible with the corroborated direct estimate of 1800 rad ($ED_{100}$) by Friedman and Perlmann (* 65). The best available empirical estimates for the radiosensitivity parameters for human skin and epidermoid and mammary cancer are given in Table I. Details of their derivation will be discussed in the following chapters.

Few attempts have been made to subject the foregoing empirical data to the rigorous statistical analyses which will enable optimal dosage to be computed with a known degree of confidence. More refined algebraic and statistical methods whereby the magnitude of the biological dosage factor 'E', as well as the biological effects of varying the three technical variables described above, can be estimated from limited data to a known degree of precision have been developed, and their derivation will also be described in the following chapters.

## SUMMARY OF CHAPTER II

The nature of radiation reactions in man is studied from the quantitative aspect, and the doses required to produce specific end-results in a vairiety of tissues and tumours are tabulated. Tissue tolerance and tumour lethal dosage levels are defined in terms of median effective doses and the associated coefficients of variation.

Six technical variables (quality, time, volume, radiosensitivity, recovery and diffusion constants) are shown to influence the reaction, and an 'iso-effect' formula incorporating these factors is proposed. This function has the general form $D = E.a.b.c$, where 'D' is the physical dose in rads, 'E' is the standard radiosensitivity factor, 'a' is a reciprocal function of the relative biological efficiency for the particular quality of radiation used, and 'b' and 'c' are functions of the over-all time and field-size, incorporating their recovery and diffusion parameters, respectively.

## SECOND PHASE - AN ANALYSIS OF THE LITERATURE RELATED TO THE QUALITY, TIME AND AREA FACTORS AND THE DERIVATION OF AN ISO-EFFECT FORMULA.

## CHAPTER III. THE 'QUALITY' FACTOR.

### RELATIVE BIOLOGICAL EFFICIENCY (RBE).

In the case of many biological objects, including most human tissues and tumours the biological effect produced by a given physical dose of radiation varies with the 'quality', or rather the energy, of the photons or particles concerned. In order to achieve a given biological response, therefore, the physical dose, as determined under standard conditions, may have to be corrected by the factor 'a' from the formula (1, 01) described in the previous chapter. This factor is, of course, a reciprocal function of the 'efficiency' of the radiation in producing the particular biological effect observed, that is,

$$a = \frac{1}{\eta}, \qquad (2, 02)$$

where $\eta$ is the relative biological efficiency (RBE) of the particular quality of radiation used. In this sense, the RBE is a function of the average 'ion-density' or 'linear energy transfer' (LET) within the irradiated tissue. This in turn depends on such physical factors as the wavelength or photon-energy, or, what amounts to the same thing, the tube-voltage, filtration, and half-value layer of the beam.

'LET' is expressed in terms of the average energy deposited in each linear unit of track of the secondary electrons, and is measured in electron-volts per micron, or, more practically, in $KeV/\mu$.

The LET-values for radiations of various qualities may be obtained by conversion of Gray's (* 72) data on specific ion-density into the appropriate units. Since the formation of each ion-pair abstracts about 35 eV from the ionising particle (* 20), the conversion factor will be of the order of .035 $KeV/\mu$, corresponding to one ion-pair per micron in

the older tables. On this basis the absolute minimum value for LET of any ionising particle obtains with the fast electrons or hard $\beta$- rays exceeding 1 MeV in energy, which have been shown to ionise at a rate corresponding to LET = 0.28 KeV/$\mu$. By comparison, the sparsely-ionising photons, such as the hard $\gamma$- rays of radium or Ta-182, have LET = 0.35 KeV/$\mu$; that for 1000 kV rontgen rays being 0.5; for 100 to 200 kV radiation around 3.0; and reaching a maximum of about 15 KeV/$\mu$ for the softest grenz-rays at a wavelength of 8.3° Å. For more heavily ionizing particles such as the protons recoiling from fast neutron bombardment, the corresponding values range between 8 and 43 KeV/$\mu$. While the massive $\alpha$- particles from polonium or radon have values of LET around 120 to 135 KeV/$\mu$ (* 172). The range of clinical interest, covering photons with energies between 10 and 100 KV, is shown in Fig 2, which is based largely on data by Gray (* 72).

The biological efficiency increases continuously with increasing ion-density, or 'LET', which in general, increases with diminishing kilovoltage. The resultant dependence of RBE on kilovoltage is not continuous, being practically constant between 20 and 100 KV, changing slowly through 200 to 1000 kV, and remaining at a relatively constant minimum at all energies above 1 MeV (* 72).

With the exception of some simpler organisms subject to 'single-hit' effects (* 115), such as viruses or bacteria, this rule seems to apply generally to metazoa, and is certainly followed consistently by all mammalian tissues. Comparable data have been obtained in such diverse tissues as Drosophila sperm, a variety of mammalian systems (* 172), as well as human skin and tumours (* 93, 149). The RBE is minimal with 'hard' radiation of low ion-density, and if we assign a value of 1.00 for the RBE of radium gamma-rays (a convenient arbitrary standard of minimal ion-density), all less energetic radiation will have RBE's greater than unity.

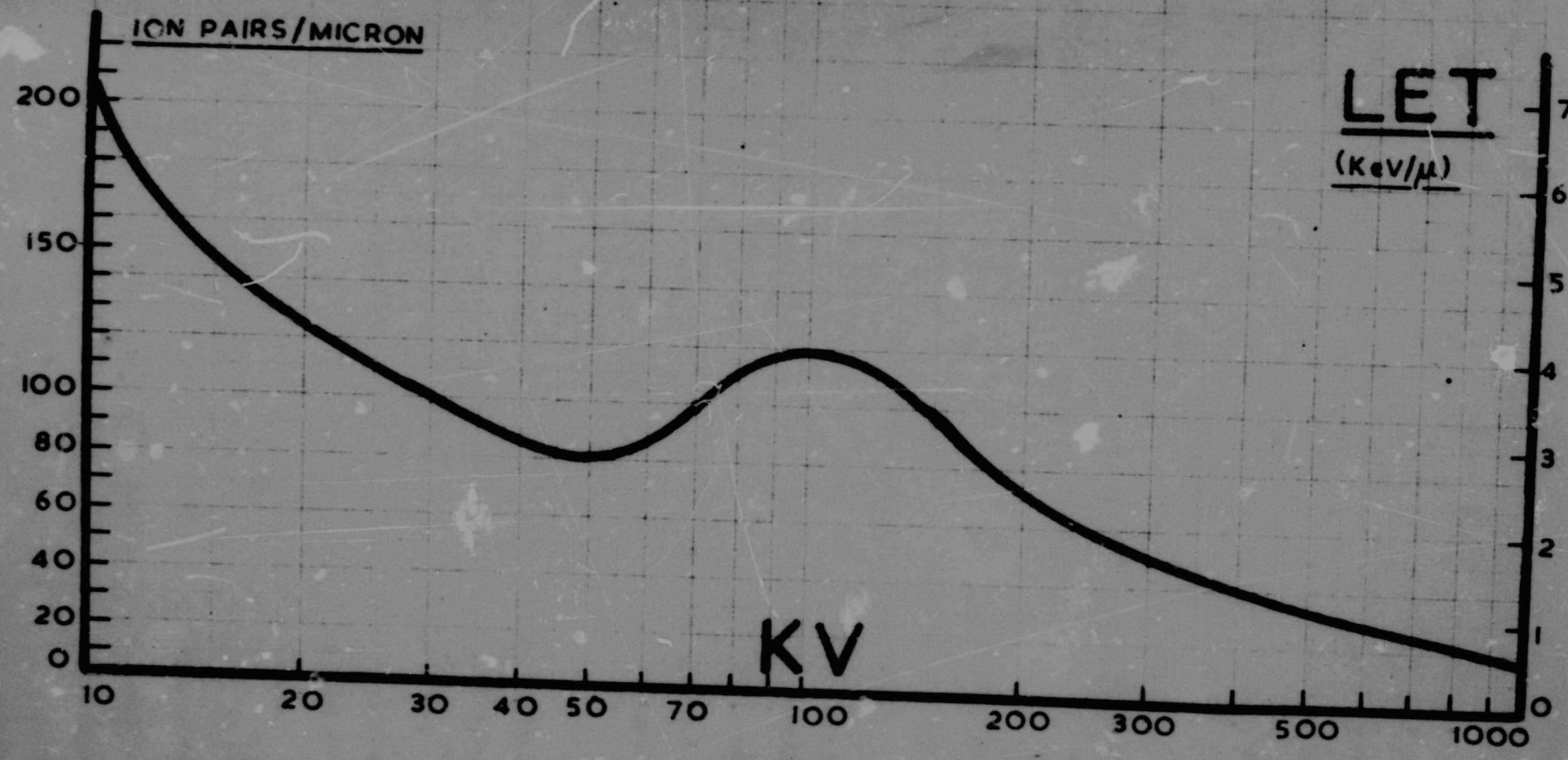


Fig. 2. Relation of Linear Energy Transfer (or of linear ion-density) to photon energy, showing increasing LET with diminishing kilovoltage. The central aberration reflects the transition from photoelectric to predominantly Compton scattering processes.

For example, under standard conditions of time and area (say a 10 cm. field given a single short exposure, taking Quimby's (* 150) data), the threshold erythema dose of human skin for gamma-rays, or for rontgen-rays of more than 1 MeV energy is 1000 rad, with 200 kV X-rays it is only 700 rad (RBE = 1000/700 = 1.4); with 140 kV X-rays it is 500 rad (RBE = 1000/500 = 2.0); and with 100 kV, or softer X-rays, it is 300 rad (RBE = 3). It will be shown that similar values for the RBE of each particular type of radiation obtain with most other mammalian tissues tested. Consistent results are obtained with such diverse end-points as tissue tolerance doses, total-body irradiation mortality, and the responses of animal and human tumours.

It is possible therefore to calculate the magnitude of the factor 'a' in formula (1, 01) from the published experimental data on RBE appropriate to the quality of radiation under consideration. A distinction should be made between the crude application of RBE as an 'order-of-magnitude' correction for personnel protection purposes, and its more refined usage in the present context as a parameter in assessing biological dosage. Under these circumstances, only comparatively recent published data could be used for the purpose of RBE determinations if serious errors are to be avoided.

Although the first reference to the concept of RBE appeared in a paper by Failla and Henshaw entitled, "Relative Biological Effectiveness of X- and $\gamma$-rays" in 1951 (* 60), it is obvious that their estimates of this ratio are invalid due to inadequacy of the methods of $\gamma$-ray dosimetry available at that time. As emphasised by Kohn (* 107), the relative biological efficiency may be defined only in terms of the ratio of equally effective absorbed doses expressed in rads. In this strict sense, the RBE is designated '$\eta$'. On the other hand, ratios of 'rontgens' do not give a true measure of RBE, and should strictly be termed the 'iso-effect exposure ratio' (designate 'e'). Provided all

the physical absorption and scatter data, including accurate knowledge of the ratio of rads per rontgen for the radiation quality used, is available, then '$\eta$' may be computed from 'e'.

Since sufficiently precise data were not available prior to the adoption of the international rontgen unit as a measure of X- and $\gamma$-rays in 1937, we are forced to confine our study of this problem to information published since 1940, that is over the past 20 years. The data summarised in Table II and Figures 3 and 4 were selected from material published during this period.

INFLUENCE OF TEST ORGANISM ON ESTIMATION OF RBE.

There is some evidence, though by no means unequivocal, that, in comparing two qualities of radiation, varying estimates of their RBE values will be obtained with different test organisms. This is an important consideration, since, if such differences are real and significant, it imposes a restriction on the type of data which may legitimately be extrapolated to the mammalian experiment or clinical situation. In extreme cases, as with 'single-hit' effects on viruses or single genes (* 115), soft radiation with large LET values has a very low efficiency compared to the less densely ionising high-energy photons; while the converse holds for 'multiple-hit' effects on whole chromosomes and most intact cells. Similarly, bacteria and protozoa may differ somewhat in this respect from metazoal animals, while other remote phyla such as plants and insects, and to a lesser extent also birds and reptiles, may give results rather different from those obtained in mammals.

We are of course primarily concerned with the reaction of mammalian tissues, and fortunately within this group at least, recent estimates of RBE have been sufficiently consistent for all practical purposes.

INFLUENCE OF PHYSIOLOGICAL STATE ON RBE.

It has been shown (* 177) that the radiosensitivity of single cells, as well as the degree to which this sensitivity is influenced by quality factors, depends on functional conditions pertaining at the time of irradiation. In particular, the radiosensitivity varies according to the phase in the mitotic cycle at which the cell is irradiated. In this way, the RBE may come to depend upon the physiological status of a cell. Under special circumstances such as the synchronous mitotic rhythms produced by irradiation with certain critical fractionation schemes, or by prior exposure to mitotic poisons, this factor might conceivably affect our estimates of RBE for various radiation qualities. It seems, however, that such effects are unlikely to be significant with complex tissues or multicellular organisms under ordinary conditions of treatment.

EFFECTS OF SUBSIDIARY FACTORS ON ESTIMATION OF RBE.

There is also some doubt as to whether the RBE can, in fact, be expressed as a single factor for the radiation in question in view of the possibility that it might depend on such subsidiary variables as the type and degree of biological damage, the absorbed dose, dose-rate, manner of fractionation, oxygen tension, pH, and temperature (* 94). The latter three factors are of course constant in most mammalian tissues and can safely be ignored. However, in assessing the relative biological efficiency of one type of radiation compared with another, it is important, particularly in the case of skin erythema studies, that the two techniques be matched so as to eliminate spurious differences due to physical 'transition zones', or to interfering biological factors such as 'volume effects' in tissues adjacent to the irradiated regions.

Specifically, the following six factors require special considerations:

(1) Absorption Effects.

With low-energy radiation, the amount absorbed in overlying inert substances (the keratinised layer in skin erythema studies, for example), should be known, so that the true 'absorbed dose' reaching the reacting tissue can be calculated. If this correction is not made a spurious underestimation of the RBE can occur with very soft radiation, the dose received by the living basal cells being considerably smaller than that incident on the superficial keratinised layers.

(2) Electronic Equilibrium.

At very high energies one must consider the effect of the predominantly forward scatter in relation to the range of the secondary electrons. When the beam is allowed to impinge upon the skin or other object tested, without intervention of 'bolus' or scatter material, the 'given dose' estimated at the electronic equilibrium may be several millimeters below the surface (* 182). The apparent 'erythema dose' would then seem to be considerably greater than its true value, giving an underestimate of the RBE. It is necessary, therefore, to interpose between the source and the test-object a layer of unit-density scattering material sufficiently thick so that the peak of the depth-dose curve coincides with the plane of the tissue tested, thus ensuring full electronic equilibrium at that plane. Alternatively, the actual absorbed dose at the point of interest, as distinct from either the maximum or the 'exposure' dose, should be calculated.

(3) Atomic number.

A spurious 'quality' effect will be detected if the average atomic number of material in the irradiated region differs from that of normal soft tissue. The large photoelectric absorption coefficient for low-voltage radiation of bone or other calcified tissues, and also, to a lesser extent, of the sulphur content of the skin, gives a greater effect with softer radiation which would exaggerate differences in RBE.

Thus the atomic number of all materials, applicators, or containers adjacent to the irradiated tissue should be tissue-equivalent or air-equivalent or, where the difference is an integral part of the tissue concerned (as in bone), appropriate corrections should be made for estimating absorbed dose in the cells concerned.

(4) Quality change in depth.

Quality changes in the transmitted and scattered components of a beam of radiation as it penetrates to substantial depths in soft tissue may also introduce a real change in RBE. The changing wavelength of the transmitted and scattered radiation as the beam traverses tissue-like materials were first fully described by Clarkson and Maynecord in 1939 (* 36). In the case of the more energetic rontgen- or $\gamma$-radiations generated by exciting voltages in excess of 250 kV, there is a progressive degradation or 'softening' of the beam with increasing depth in tissue (* 169), with a corresponding increase in its biological efficiency (* 28). Conversely, there is also some 'hardening' in depth of heterogeneous low-energy beams (under 100 kV) due to the extra filtration afforded by the overlying tissue (* 169). The importance of allowing for this effect in treating deep-seated tumours will be discussed below. Thus experimental determinations of RBE are likely to remain valid only in the case of relatively superficial tissues, or in superficially placed test organisms or objects exposed exclusively or mainly to the incident beam.

Biological effects which may vitiate the accuracy of an RBE determination arise from difficulties in matching time and volume factors with different sources and generators.

(5) Time factors.

With some types of equipment it may not be possible to avoid delivering radiation at a dose-rate very different from that of the reference standard. A radium applicator, for example, is likely to take some hours to give a dose which a rontgen generator would deliver

in minutes, so that recovery processes could introduce a virtual decrease in RBE. At the opposite extreme, radiation from betatrons and linear accelerators is delivered in frequent microsecond pulses at a very high instantaneous dose-rate. At these great intensities, the large instantaneous concentration of ions in the tissue could produce secondary chemical effects characteristic of high ion-density radiation, resulting in greater biological effects, and hence, a real increase in the RBE (* 24). Averaged or smoothed dose-rates should naturally be at least approximately the same in any controlled comparison.

(6) Geometrical factors.

The size and shape of the irradiated volumes should, of course, be matched as far as possible in comparative groups, or one technique, say a radium applicator compared with a rontgen beam, may give a very different gradient below skin level and hence introduce a volume or field-size effect even though surface portals are comparable. By adjusting focus-skin distances, it has, in some investigations (* 195), been found possible to match the depth-dose curves of the two qualities under survey. On the other hand, with sufficiently 'soft' radiation, the depth-dose is such that only a very thin slab of skin, having a small ratio of volume: bounding-surface might be irradiated. This would diminish the intensity of the reaction, or require larger doses to give a standard reaction, and thus result in a marked underestimation of the RBE. Such a volume factor probably explains why published figures for 'grens-ray' irradiation of human skin (* 195) show an apparent reversal of the general trend to greater effects with low voltages, the erythema dose being apparently much larger than with the more penetrating conventional 'superficial' radiation. When the appropriate corrections for the 'absorption' and 'volume' factors are introduced, the RBE remains around a value of 3 for 'grens-rays' and, indeed, for the whole of the low-energy range (Fig. 4).

In a series of experiments carefully designed to eliminate physical transition zones and similar discontinuities, and using the true absorbed dose in the appropriate analysis, Storer, et al. (* 172) observed that the over-all variation of RBE with LET was considerably smaller than that given in many less rigorously controlled series. Since their analysis covers nine different qualities of radiation ranging from $\gamma$-rays at 0.3 KeV/$\mu$ , to heavy recoil particles at 850 KeV/$\mu$ , each tested on several of ten alternative biological responses in rodents, these estimates can probably be accepted as the best available at the present time.

A summary of all relevant published information on comparative RBE values in relation to LET, using true estimates of '$\eta$' whenever the data is adequate, is given in Fig. 3. The open lettered columns refer to individual reports; the solid bars are averaged values for each particular quality range; and the solid curve has been fitted empirically to these points. It will be noted that, in spite of their diverse origins, the various observed data are in fairly good agreement at least in the range between 0.3 and 30 KeV/$\mu$ . Beyond this range, however, where heavily ionizing entities such as slow neutrons, $\alpha$- particles, and recoil nuclei are concerned, there are very large discrepancies as shown in the dotted right-hand section of the curve. It is probable that the concept of RBE as a single measure is no longer applicable at very high ion-densities, where the biological injury must be discontinuous and heterogeneously distributed in space and time. Fortunately, the range of clinical interest falls within the relatively well-determined low-density region.

'RBE' FOR HUMAN TISSUES.

As a general rule, studies on human tissues and tumours exposed to ionizing radiations of various ion-densities are also in agreement with the curve given in Fig. 3, and indeed skin erythema doses for high-energy $\gamma$-rays, 200 kV rontgen rays, and fast neutrons have in fact been incorporated in the data. One significant discrepancy, however, which cannot be resolved on the basis of irregularities in the

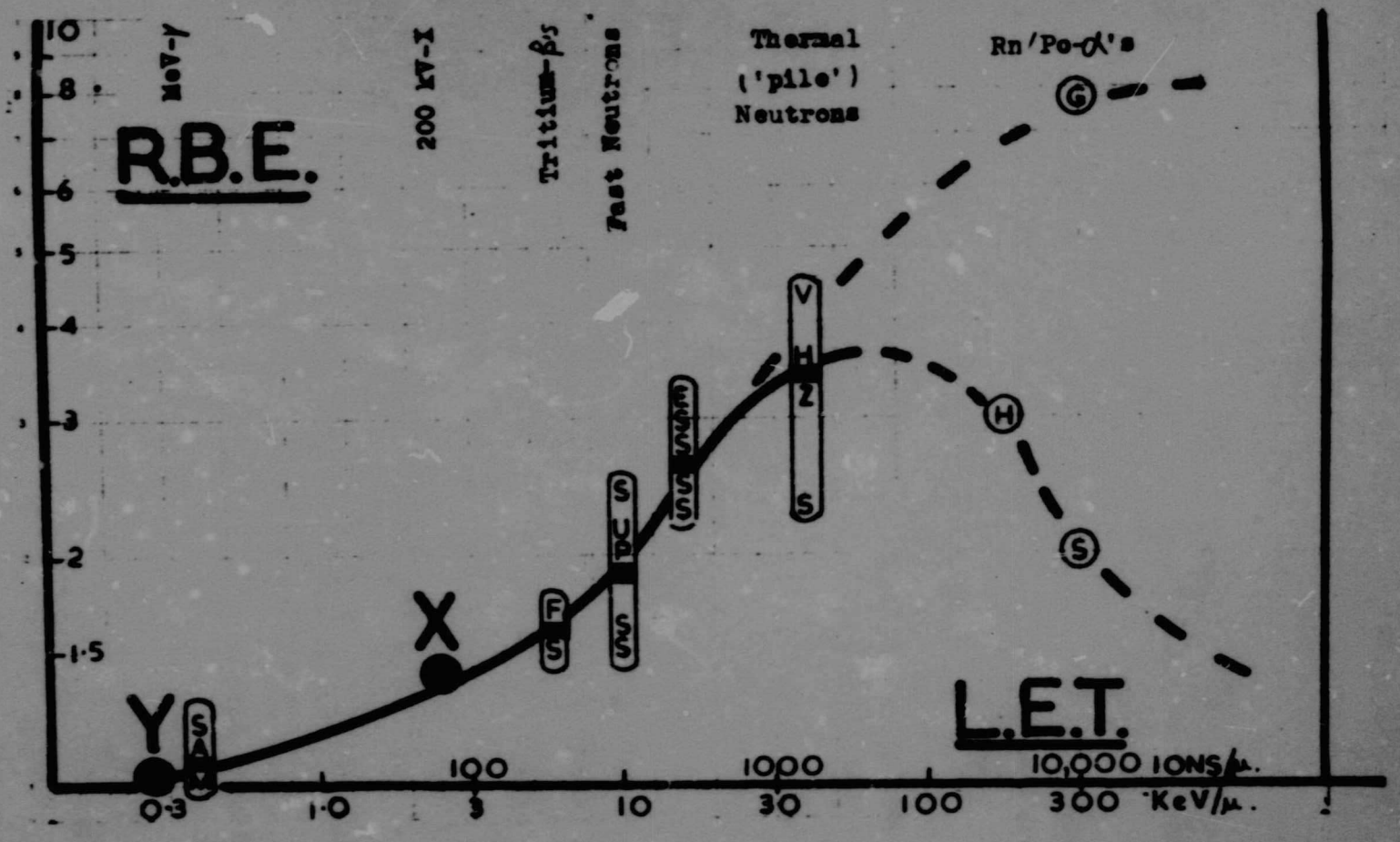


Fig. 3. Dependence of R.B.E. on L.E.T. for a wide range of ionizing particles. Y = Point of minimal ion-density taken as unity; X = Averaged RBE data for roentgen rays at 100 to 250 kV.

absorbed dose per se, remains. At the 'soft' end of the rontgen-ray spectrum, with half value layers under 0.3 mm Cu, the RBE estimated from human skin reactions is consistently greater than that obtaining in the laboratory experiments. Furthermore this apparent RBE in human skin of soft rontgen-rays is higher than that of corpuscular radiations at identical ion-densities. In this range, the observed skin erythema doses heavy line in (Fig. 4) approaches 300 r ($\eta = 3.3$), while the value to be expected on the basis of the experimental data from Fig. 3, corresponding to the thin line shown in Fig. 4, would be at least 500 r ($\eta < 2$).

The difference is probably due to the higher mean atomic number, and increased absorption coefficient, of skin associated with its greater-than-average sulphur content. This factor, besides giving a significantly greater absorbed dose in the skin, would also effect a difference in the relative proportions and average energies of photo-electrons and Compton recoil particles. The over-all result would be an appreciable increase, real or apparent, in RBE of the softer radiations with respect to human skin, over and above that attributable to LET per se.

PRACTICAL ASSESSMENT OF THE FACTOR 'a' IN TERMS OF 'RBE'.

Among the many possible 'quality' factors used to describe a beam of radiation, the following physical parameters could be considered as functions of RBE: The effective wave-length, frequency or quantum-energy of rontgen or $\gamma$-rays; the exciting peak kilo-voltage, or average energy in MeV of photons or ionising particles; the absorption coefficient or half-value layer in given absorbing material; specific ion-density (ion-pairs/micron) in tissue or equivalent absorber; and linear energy transfer (LET, in KeV/$\mu$).

Of these, the LET gives the most rigorously established measure for those physical events immediately preceding the biological injury.

It is generally valid for all types of radiation and for all degrees of biological action, including excitatory as well as ionizing events. There is, however, still a considerable lack of agreement and precision in our knowledge of the physical data required for accurate estimation of LET as an absolute quality (* 30). Similarly, knowledge of specific ion-density depends upon estimates of physical constants which are by no means well-determined (* 46).

Of the remaining three quality factors, that most readily measured and assessed in the wide variety of generators, sources and filters used in clinical radiation therapy, is the absorption coefficient or half-value layer. Since we are here primarily concerned with the RBE of rontgen and $\gamma$-ray photons of clinical quality, we shall henceforth refer the RBE comparisons exclusively to the half-value layer in copper of the incident beam.

Furthermore, in clinical radiation therapy, only that range of LET applicable to photons and their secondary scattered particles need be considered. This corresponds to the fairly well-determined left hand limb of the curve in Fig. 3, ranging from 6 to 300 ions, or 0.3 to 10 KeV, per micron. For practical purposes, therefore, the curve in Fig. 4, based upon skin erythema studies and indicating the apparent RBE (as distinct from the true '$\eta$') in relation to the half-value layer of the beam in copper, would seem most appropriate for the purpose of computing the factor 'a' in the iso-effect formula.

The heavy line in Fig. 4 represents the best available estimate for the function relating the half-value layer in copper to relative biological efficiency, or its reciprocal, the skin erythema dose expressed in surface rontgens. Strictly speaking the 'rad' is not the appropriate unit in this context unless the small discrepancies in atomic number, absorbtion coefficients, and ionization energy of skin can be taken into account.

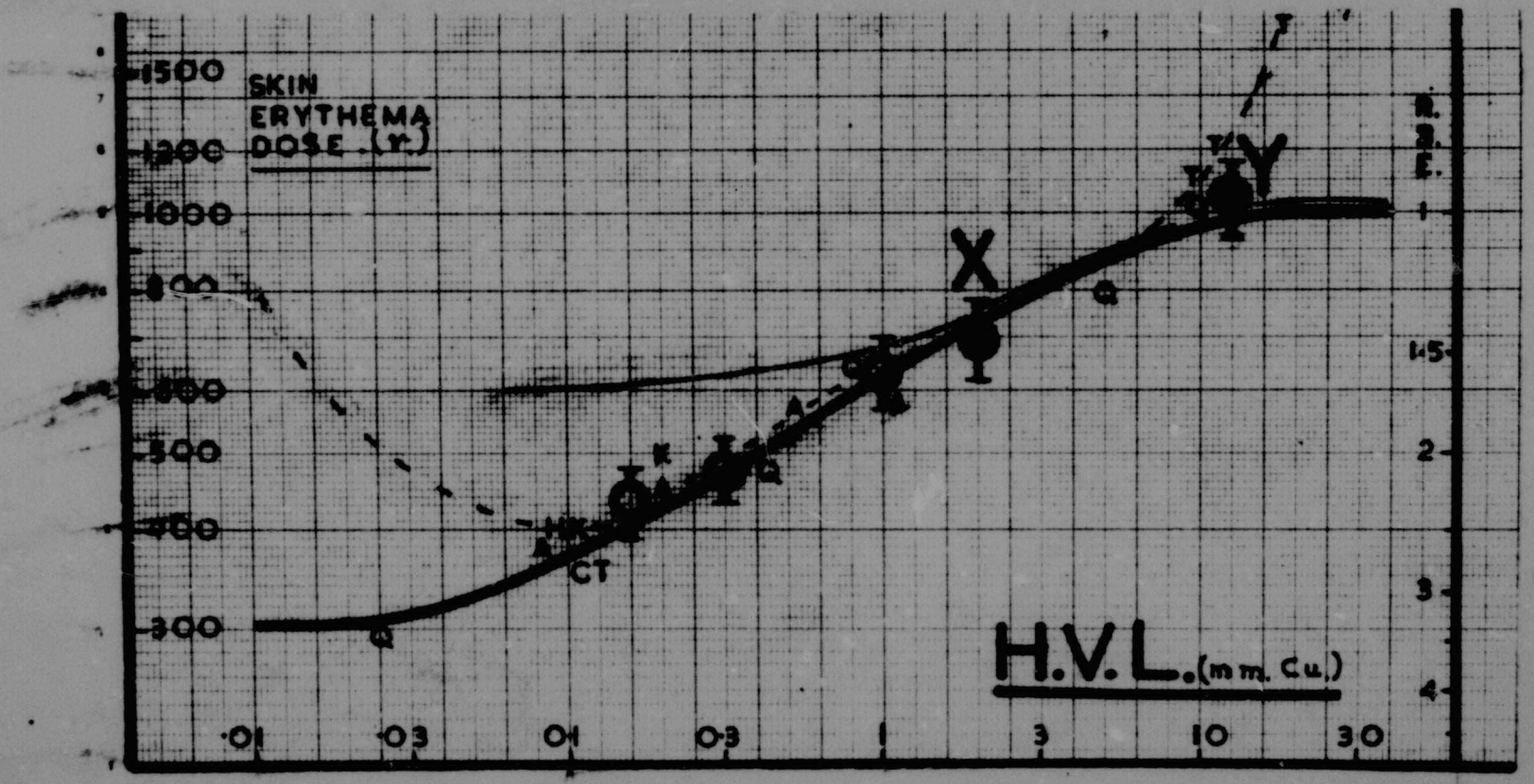


Fig. 4. Relation of Skin Erythema Dose, a reciprocal function of RBE, to quality (half-value layer) for a wide range of photons. Lettering refers to authors quoted. X and Y represent the X-ray and radium standards respectively.

The lettering in Fig. 4 refers to published data on skin erythema by Andrews (* 6), Mackee (* 121), Quimby (* 149), Tod (* 181), and Trump (* 183), respectively. The larger circles represent the writer's estimates (* 44) of median erythema doses, and their associated confidence limits, for radium $\gamma$-rays, and the high-, medium-, and low-voltage rontgen rays as used in clinical radiation therapy.

The solid thin line shown the corresponding values (in rads) assessed from experimentally determined estimates of '$\eta$', indicating the good agreement with erythema studies in the higher energy range but the significant discrepancies in the case of softer radiations. The dotted line shows the large errors in apparent skin erythema doses if 'transition effects' (absorption and electronic equilibrium) are neglected.

## COMPARATIVE RBE OF 'MEGAVOLTAGE' AND 'CONVENTIONAL' RADIATIONS.

In addition to the data of Fig. 4, many independent experimental and clinical comparisons have been made between 'megavoltage' radiation ($\gamma$-rays from telecurie equipment as well as bremstrahlung from accelerators operating at 1 to 4 MeV) and the so-called 'conventional' rontgen rays in the 200 to 250 kV range.

The International Committee on Radiological Units (* 94) had recommended using 200 kV rontgen rays with a specific ionization of 100 ions/$\mu$ (LET = 3 KeV/$\mu$), at a dose-rate of about 10 rad/min., as a standard of reference. However, in this energy range particularly, small variations in quality result in significant differences in the relative magnitudes of photoelectric and Compton absorption processes in various tissues, and hence lead to large and possibly spurious variations in biological efficacy. At the high-energy range, however, where the ion-density approaches the theoretical minimum (* 72), large variations in quality, say from $10^6$ to $10^8$ eV, have no perceptible

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**Name of thesis** Radiation Parameters 1960

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