of tumours cured in that group. The circles represent the median dose for each group, and the smooth curve drawn through them is probably the true curability curve for epidermoid cancer. It is of interest to note that in the highest dosage range the curability is considerably less than expectation. This deviation is associated with the cases of 'necrosis plus recurrence', and confirms the existence of the supralethal effect described by Paterson (# 138).

In Fig. 16b the same data are charted on lognormal probability co-ordinates, the ordinate representing the percentage cured. The straight line obtained proves the almost perfect lognormality of the grouped data. The mean lethal dose is seen to centre around the E = 3000 (in fair agreement with previous estimates, Table I), the standard deviation (S) being about 400, whence U = 1.13 and the 5%-uncertainty factor is 1.28.

The appropriate factor for the tumour curative dose (LD-98) is, therefore, 3000 x 1.28, correspondong to E = 3900 for γ-rays (η = 1.00) or almost 2000 rad in a single application of medium voltage therapy (η = 0.5). This latter dosage is, of course a well-established clinical datum.

The inset in Fig. 16, illustrates a method for determining the recovery exponent (n) by a graphical solution. Various values of 'n' ranging from zero to 0.5 were selected, and the resultant estimates of biological dose tabulated in a manner similar to Table IX, but re-grouped accordingly. The cure-rates so obtained were similarly charted on lognormal probability graphs, and the value of 'U' corresponding to each value of 'n' was determined. It is seen that 'U' is a minimum as 'n' approximates 0.25. The disadvantage of this graphical method, which is otherwise simple and sufficiently accurate for practical purposes, is that it furnishes no means for computing the variance of 'n'. It is, therefore, impossible to test the agreement between our rough estimate of n = 0.25, and the corresponding results from other

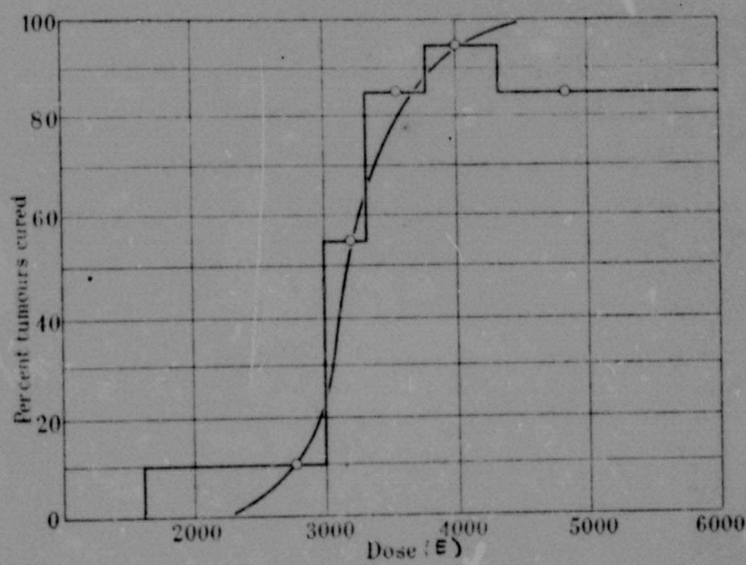


FIG. 16(a)—Cumulative frequency diagram illustrating increased proportion of tumours cured with increasing biological dosage. Doses are expressed in ~~[illegible]~~ terms of the 'severity' parameter 'E'.

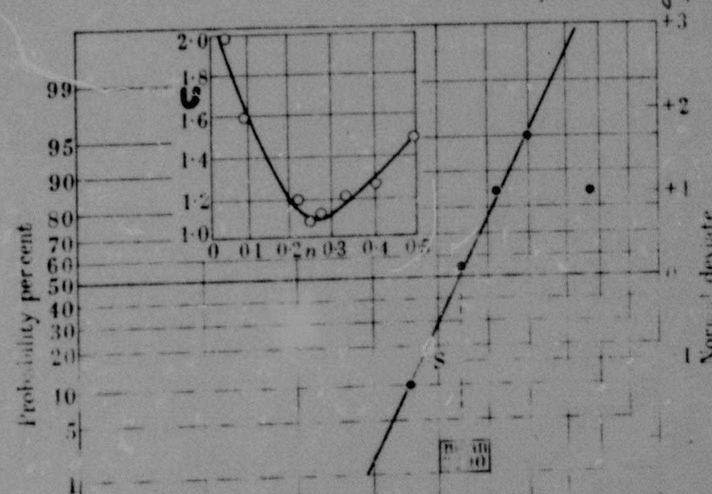


FIG. 16(b)—Test for lognormality of the tumour dosage data. The outlying point on the right illustrates the "supralethal effect." The inset demonstrates a method for determining the recovery exponent (n).

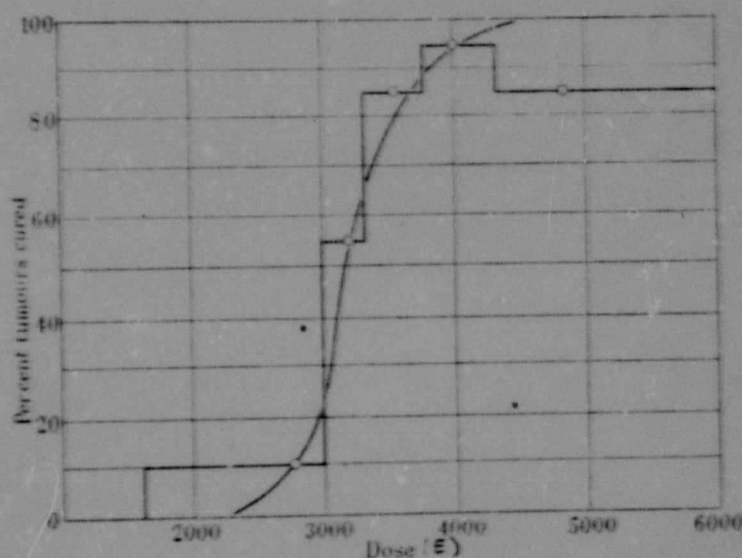


FIG. 6(a).—Cumulative frequency diagram illustrating increased proportion of tumours cured with increasing biological dosage. Doses are expressed in ~~[illegible]~~ [illegible] of the [illegible] parameter E.

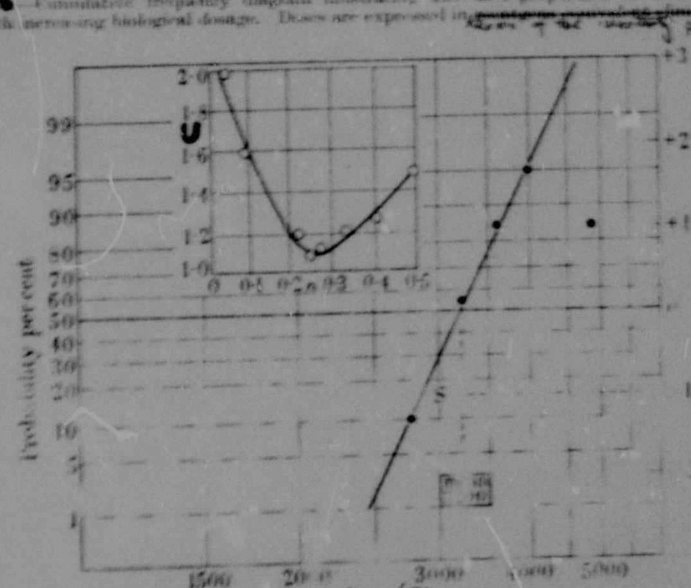


FIG. 6(b).—Test for log-normality of the tumour dosage data. The outlying point on the right illustrates the "exponential effect". The inset demonstrates a method for determining the [illegible] exponent (p).

sources which have been shown to average n = 0.22. By Kerrich's (* 104) rigorous method this value is estimated to lie between 0.24 and 0.34.

Kerrich's (* 104) method for evaluating the foregoing data algebraically leads to the following theorem. The data in Table IX "suggest that the 'standard or biological' dose = Physical dose x RBE ÷ T^n, or E' = D'/T^n say, where E' = biological dose, D' = dose x RBE, and T = time in days. If E' is the exact 'dose', suitably standardised, necessary to effect a cure, then a reasonable assumption is that log E' = log D' - n log T is normally distributed. Writing e = log. E', d = log D', t = log T, this hypothesis becomes e = d - nt is normally distributed with, say mean μ and variance σ^2.

"To study the question of reliability we must employ an algebraic method for estimating these values. The problem is, in principle, reminiscent of one examined in Finney's 'Probit Analysis' (* 61) (p. 106. Ex. 18), and adapting the algebraic methods explained in Appendix II of that book, the following results were obtained for the series of tumours described:

	μ	n	σ
Estimated value.	.3.4642	.2893	.0709
Estimated standard deviation	.0359	.0285	.0186

The sizes of the estimated standard deviations show that none of the constants can claim to be very 'well determined'.

"In more detail, the estimated covariance matrix is:

var. (μ) = .001292 cov (μ, n) = - .000955 cov (μ,σ) = - .000383

var (n) = + .000813 cov (n,σ) = + .000227

var (σ) = .000348

The mean value of e is μ. We estimate that this lies between 3.4642 ± .0718 with 5 per cent risk. This makes our estimate of median E' to be 2912 with a 5 per cent uncertainty factor of 1.180.

"If ϱ is greater than $\mu + 2\sigma$, then the cure rate should be 97.5 per cent or more. Our estimate of $\mu + 2\sigma$ is 3.6060 ± .0679, and the corresponding biological dose is E' = 4036 with a 5 pe[illegible]nt uncertainty factor of 1.169."

THE THERAPEUTIC RATIO IN CLINICAL RADIATION THERAPY.

The concept of a 'therapeutic ratio' has been adopted in radiotherapy, as in the case of therapeutic chemicals, so as to give a measure of the degree to which the largest safe tolerance dose exceeds the minimum effective dose. The ratio indicates the general value, and particularly, the 'margin of safety', of a given procedure. In radiotherapy, it could be defined as the ratio of tissue tolerance to tumour lethal doses. However, both of these quantities are subject to individual variation and depend on technical variables and statistical parameters. In other words, the therapeutic ratio in radiotherapy is a ratio between median values, or some other acceptable measure of 'position', of two sigmoid curves, corresponding to the probability of necrosis and of cure, respectively.

A therapeutic ratio considerably greater than unity is essential in clinical radiotherapy, and, in general, the bigger this ratio, the better the chance of cure. Since skin tolerance and tumour lethal doses depend upon the many technical variables described, it is possible to control the therapeutic ratio within fairly wide limits by a judicious choice of factors, particularly the field-size and the over-all time. However, the statistical data derived (in the previous chapter), giving median values for tumour lethal and skin tolerance doses, are insufficient for the purpose of specifying optimal treatment factors in the clinical prescription, in which it is mandatory simultaneously to exceed the median lethal tumour dose by the lar[illegible]acticable amount and yet fall short of the minimal necrotis[illegible]se by the greatest possible margin.

The acceptable 'maximum tolerance' dose must carry no more than a nominal risk, say under 2%, of necrosis, while the 'tumour lethal' dose must have a similarly small rise of recurrence. That is, the two doses must be at least two standard deviations below and above the respective medians. The actual difference between median curative and necrotizing doses, therefore, should exceed four standard deviations.

In order to estimate the actual magnitude of the therapeutic ratio in the case of a specific tumour treated in site within a particular organ or tissue, one would have to assess the individual radiosensitivities including the effects of all the technical variables, of both the tumour and the normal tissues constituting its bed, as well as certain factors pertaining to the interaction between them.

For the purpose of these calculations, one requires that no less than 11 factors be clearly defined and specified for the conditions of treatment. In addition to the 3 independent variates already described (relative biological efficiency, over-all time, and field-size), there will be 3 associated parameters (the standard radiosensitivity of the tissue, the recovery exponent, and the diffusion exponent) for both tumour and normal tissue, making 6 parameters in all. The calculation is also affected by the coefficient of variation, or more precisely the <u>standard uncertainty factor</u> (U), a measure of the individual variation among patients, and by the <u>heterogeneity factor</u> (H), the ratio of maximum tissue dose to minimum tumour dose.

The <u>uncertainty factor</u> permits one to calculate the dosage required to produce greater or lesser frequencies of response from the given median values. This factor generally has a value of about U = 1.11 to 1.14, and is approximately the same for normal tissues and tumours, which means that in about 95% of cases the radiosensitivity does not differ from the median value by more than a factor of $U^2 = 1.30$, or roughly twice the coefficient of variation, say ± 30%. Thus, increasing the LD-50 by a factor of 1.30 gives the 98% lethal dose (LD-98). Similarly, decreasing the LD-50 by the same factor gives the 2% lethal dose (LD-02). The median exudative dose (herein termed XD-50), producing the so-called third-degree reaction in at least half the treated cases, is, for practical purposes, identical with the generally accepted skin tolerance limit in clinical radiotherapy. Since XD-50 = 3/4 ND-50 (Table I), which is roughly equal to $ND\text{-}50/U^2$ = ND-02, incidence of necrosis to be expected through accepting the XD-50 as a practical tolerance dose is about 2%, which for reasons to be given below, is often the irreducible minimum risk unavoidable in curative radiotherapy.

THERAPEUTIC RATIOS IN RELATION TO PROGNOSIS.

Corresponding to the various levels of dosage described in the preceding section, the following set of 'therapeutic ratios' can be derived, and applied in the appropriate situations. If one takes the ratio of median necrotising and tumour lethal doses, that is ND-50/LD-50, and designates this value θ, then the ratio of the tolerance limit to the median lethal dose, that is XD-50/LD-50, is equal to θ/U^2. This latter ratio, which was termed the therapeutic ratio in previous publications (* 39, 44) is here recognised as a special case from a family of related functions. Similarly, it may be of interest to consider the ratio of 'tolerance' and 'curative' doses, or ND-02/LD-98, which equals θ/U^4, for if this value exceeds unity it becomes possible to deliver a dose giving 98% probability of tumour regression with no more than 2% risk of necrosis, so that the total probability of uncomplicated cure approaches a theoretical maximum of 96%.

It will be realised that there is, in this reasoning one assumption which may not remain valid under all circumstances. It was assumed that the tumour and the normal tissues concerned in assessing the therapeutic ratio received the same dose of radiation. In practice, of course, the overlying skin or some other tissue or organ frequently receives a greater dose than that reaching the tumour. This heterogeneity will, in effect, diminish the therapeutic ratio and worsen the prognosis. To allow for this factor, another type of therapeutic ratio is required; namely, the ratio of median S corrected for heterogeneity, that is ND-50/H(LD-50), or θ/H. Here H is the heterogeneity factor, defined as the ratio of maximum tissue dose to minimum tumour dose, and may, at least in the case of external beam therapy, be looked upon as a reciprocal function of the percentage depth dose at the tumour. This factor consequently permits one to define given maximum doses in terms of tumour lethal doses, or conversely, tumour depth doses in relation to the skin tolerance limit. The importance of this particular ratio lies in the fact that the prognosis, expressed as a probability, can be shown to be a mathematical function of this factor.

The probability of cure at any given <u>tumour dose</u> depends on the factor by which that dose exceeds the LD-50, and is given by the 'normal deviate' (δ) in the expression

$$D = (LD\text{-}50) \cdot U^{\delta} \qquad (3, 23)$$

Where 'D' is the tumour dose and 'U' the standard uncertainty factor as defined previously. Taking the skin tolerance limit (XD-50) as the maximum permissible dose, it follows that the tumour dose cannot exceed

$$D = (XD\text{-}50)/H$$

Where 'H' is the heterogeneity factor. From these two equations

$$H . U_t^{\delta} = \frac{(XD\text{-}50)}{(LD\text{-}50)} = \frac{\theta}{U_s^2} \qquad (3, 24)$$

where U_s and U_t are the uncertainty factors for skin and tumour responses respectively. It may be assumed that $U_s = U_t$, which is approximately true in most instances, and the expression (3, 24) then simplified to read

$$\theta = H . U^{(\delta + 2)}$$

whence

$$\delta = \frac{\log \frac{\theta}{H}}{\log U} - 2 \qquad (3, 25)$$

Since the divisor in equation (3, 25) is constant for any given tumour species, δ is directly proportional to log (θ/H). It is then possible to calculate 'δ', and determine the associated probability level. The probability of cure, corresponding to any given value of δ, can be obtained from statistical tables of the normal deviate or from the area of the normal curve. It will be noted that $\delta = 0$ corresponds to a cure rate of 50%; $\delta = 1$ to 84% and $\delta = 2$ to 97.7%. In this way a definite prognosis, as far as the primary growth is concerned, can be assigned to any epidermoid cancer to known size treated, over a given number of days, to the limits of tissue tolerance.

ESTIMATION OF THE STATISTICAL PROGNOSIS.

As shown in the foregoing paragraphs, the concept of 'prognosis' as applied to the local disease can be given a precise quantitative meaning in the sense of an estimated probability of uncomplicated cure with any given treatment regime. It can be computed as the probability of cure at the dose given minus the probability of necrosis at that dose. Since both probabilities are sigmoid curves, this difference should be a monophasic function with a well-defined maximum. In other words, there must exist a particular dose at which the probability of cure, that is of tumour regression without necrosis, is maximal (see Fig. 18).

It will be shown that this optimal dose lies between the two median values, and tends to approach their geometric mean. The prognosis can thus be assigned a percentage probability ranging from zero at low dosage, through the optimal dose and down to zero again at grossly excessive dosage.

It is apparent from the sigmoid curves in Fig. 17, that increasing the tumour dose should increase the probability of cure. Also following a similar sigmoid curve, the risk of necrosis increases continously with increasing tissue dose. Observed cure rates, at least for epidermoid cancer, have in fact been found (* 44) to follow

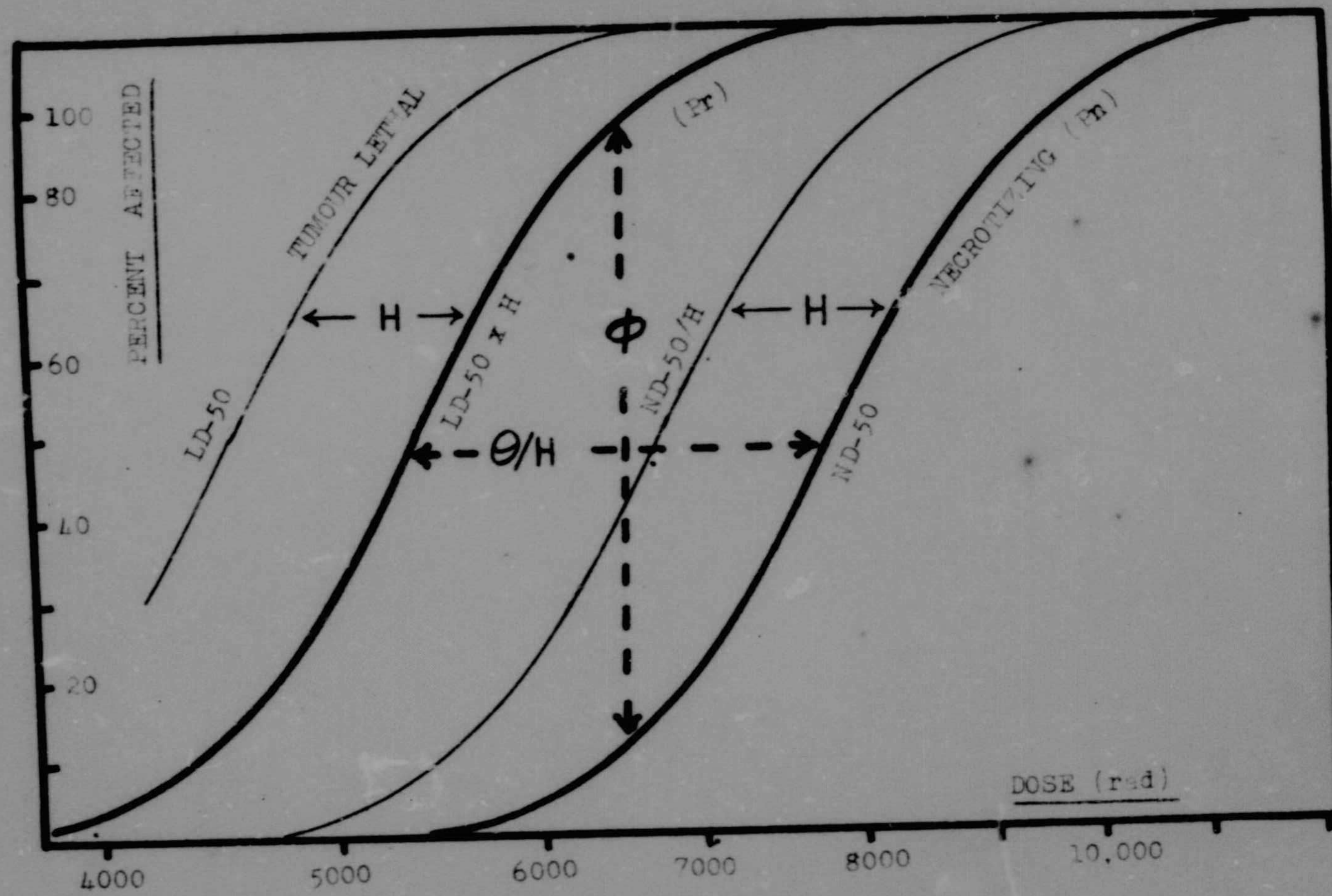


Fig. 19. Dosage-response curves for epidermoid cancer and normal tissue under the following conditions: 200 kV; HVL 1.5 mm Cu; 10 cm diameter field; 26 days over-all time; heterogeneity factor 1.2. Curves indicate the probability of tumour regression (Pr) and of necrosis (Pn).

the sigmoid curve very closely with the exception of the extreme upper limit, where, concomitant with the increasing risk of necrosis, a distinct downward trend appears. This is, presumably, a manifestation of the 'supralethal effect' (# 138) appearing as the limits of normal tissue tolerance are exceeded.

Since necrosis is, therefore, not merely an undesirable complication of overdosage, but is also associated with a tendency to recurrence of the irradiated tumour, the true dosage-response curve for the probability of local cure is a function of the difference; (probability of regression, P_r) - (Probability of necrosis, P_n). If these two probabilities are stochastically independent, the <u>prognosis</u> or probability of cure

$$\Phi = P_r \;(1 - P_n) \qquad (3,\ 26)$$

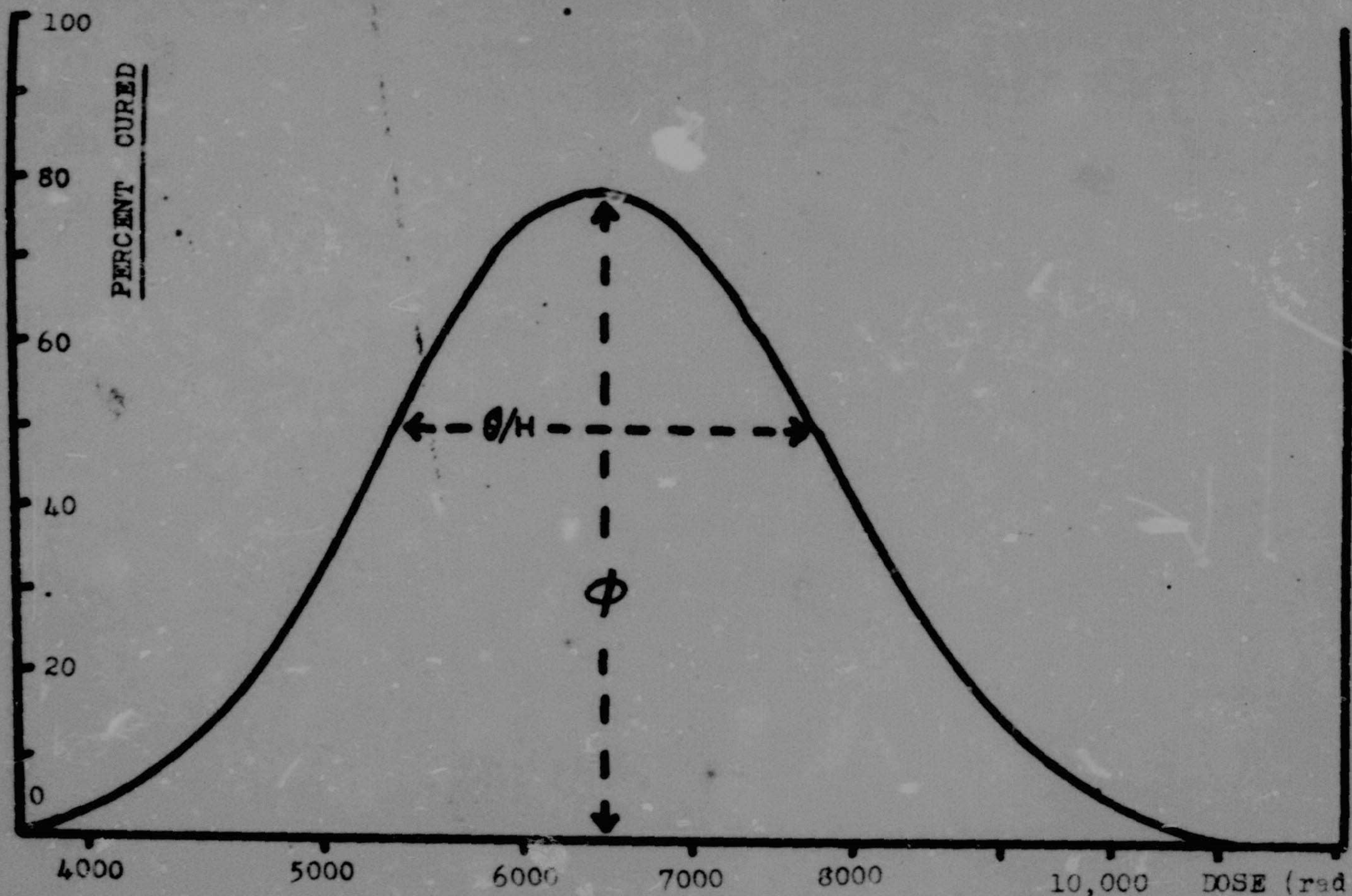
If, on the other hand, the two functions are correlated, the prognosis approaches

$$\Phi \to P_r - P_n \qquad (3,27)$$

The latter seems the more likely alternative, since the 'spread' of the curve is due, at least in part, to variation in dosage attributable to fluctuations in output of the radiation source, which would effect both skin and tumour simultaneously. At the upper range of curability, with which we are concerned in practice, there is little difference between the alternatives, though the latter, somewhat underestimating the cure-rate associated with a given procedure, tends to err on the side giving the greater margin of safety. In either instance, the estimated prognosis follows a symmetrical monophasic curve (Fig. 18) with a single maximum whose position is readily computed and indicates the theoretical optimum dose.

Assuming the second alternative and the log-normal distributions previously suggested, the prognosis may then be represented as:

$$\Phi = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\xi} \epsilon^{(x-\xi)^2} - \epsilon^{(v-\xi)^2} \,.\, d\xi \qquad (3,\ 28)$$



<u>Fig. 18.</u> Prognosis as a function of dosage and therapeutic ratio, Φ = Pr - Pn . Manifestly the optimum maximum tissue dose, for the same conditions as in Fig. 17, is 6600 rad, corresponding to a minimum tumour dose of 5500 rad, giving 80% uncomplicated cures, 10% recurrence, and 10% necrosis.

where ζ, χ, V, and σ respectively represent the logarithms of the given dose (D), the median tumour lethal dose (LD-50), the median necrotising dose (ND-50), and the standard uncertainty factor (U) previously described. It then follows that the function reaches its maximum when $\chi + V = 2\zeta$, that is when the given tissue dose is the geometric mean between the LD-50 and the ND-50.

While the <u>position</u> of the peak, indicating the optimal dose for a given set of treatment factors, can be determined in the foregoing manner, the <u>height</u> of the peak, representing the probability of cure at the optimal dose calculated in this way, is dependent on the degree of separation between the tumour lethal and tissue necrotising dosage curves (Fig. 17), being therefore, a function of Θ/H. The relationship between the prognosis (Φ) and the therapeutic ratio (Θ) is illustrated in Fig. 18, Φ and Θ/H being respectively the vertical and horizontal axes of the area enclosed by the two relevant sigmoid curves (heavy lines in Fig. 17).

To any given value of Θ/H there corresponds a definite maximum prognosis (Φ_{max}). The function can be solved by using tables of the probit transformation, so that the prognosis or chance of cure, given the optimal dosage appropriate to the circumstances, can be computed. The relationship of Φ_{max} to Θ/H is shown graphically in Fig. 19. It will be noted that a value of Θ/H = 1.5 corresponds to a possible cure rate of 90%.

The existence of specific optimal doses giving maximal cure-rates, both larger and smaller doses giving worse results, has been reported in several clinical series, and confirms the general validity of the foregoing theory.

The first practical applications of this concept appear in papers by Tod (* 180) and by Garcia (* 67) in 1943, on tissue dosage

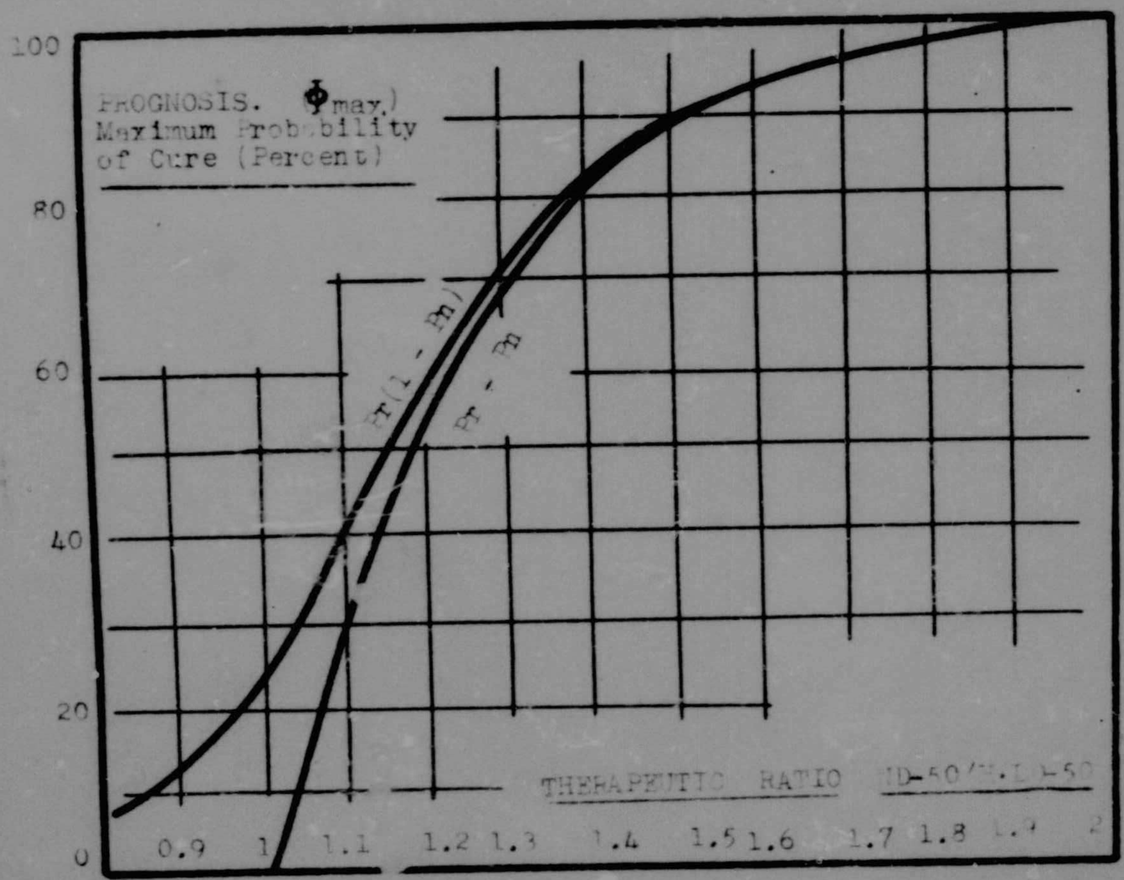


Fig. 19. Prognosis as a function of therapeutic ratio, when 'regression' and 'necrosis' are assumed to be (a) stochastically independent, P_r ... and (b) fully correlated, ($P_r - P_n$).

control of carcinoma of the cervix. Antedating Strandqvist in this regard, Garcia introduced corrections for both quality and time factors in his comparisons and demonstrated the existence of an optimal dosage level for this tumour. Subsequently, similar monophasic response curves were obtained by Nolan, Costolow and Du Sault (* 134) and by Paterson (* 139), in their independent series of uterine cancers.

While the exact magnitudes of these optimal doses in other situations have yet to be determined empirically, it is possible by statistical analysis of the distribution of radiosensitivity among normal and malignant tissues in various individuals, to compute these quantities theoretically. Such values should, pending their experimental verification, furnish clinical dosage standards giving the best results obtainable with present day techniques.

SUMMARY OF CHAPTER VI

The validity of the iso-effect formula is reconsidered as a physical or mathematical model system, and it is shown that the hypothesis of a single exponentially decaying 'substance' is untenable. A heterogeneous mixture of such substances could give a satisfactory, though much more complex, function, but this is found to fit observed data little better than the simple empirical iso-effect formula given. A least-squares regression of skin reaction intensity upon dosage, and a probit analysis of tumour dosage data, gave estimates for the empirical parameters virtually identical with those obtained from published data. The analysis introduces the therapeutic ratio as a strict biometrical concept, and the statistical prognosis (probability of uncomplicated cure) is shown to a function of this ratio.

CHAPTER VII. CLINICAL RADIATION DOSAGE.

COMPUTATION OF THE OPTIMAL DOSE.

The theoretical and statistical principles of radiation therapy developed in the preceeding sections should permit one to compute precisely the optimal skin and tumour doses appropriate to a given clinical problem. In most situations there can be only one optimal dose giving the maximum probability of uncomplicated cure, that is the highest chance of tumour regression compatible with a minimal risk of necrosis.

In Fig. 20 are shown a series of prognostic curves derived in the same manner as that of Fig. 18, for epidermoid cancer treated under a variety of conditions: with fields of 2, 5, 10, and 20 cm diameter; over-all times of 1 day, 1 week (5 days) and 1 month (26 days); and a heterogeneity factor of 1.2 in each case. Several facts, well-established from clinical experience, emerge directly from these computed curves and thus confirm the general validity of the formulae.

With fields not more than 2 cm in diameter, satisfactory cure-rates are obtainable with single treatments, the optimal maximum dose being 2500 rad with superficial therapy. With larger fields longer treatment times are desirable; a week is required for fields up to 5 cm in diameter, and over a month with 10 cm fields. It is expected, in fact, that the optimum over-all time should vary roughly as the cube of the field diameter, equivalent therapeutic ratios obtaining with fields of 2½ cm treated in one day, 5 cm in 1 week, and 8 cm in 1 month. For 1 week the optimal dose appears to be 4500 rad high-voltage rontgen rays or 7000 rad with radium, and for 1 month about 6500 rad high-voltage rontgen rays maximum tissue dose. Since the estimates were based on heterogeneity of H = 1.2, absolute minimum tumour doses may be 20% below these computed maxima.

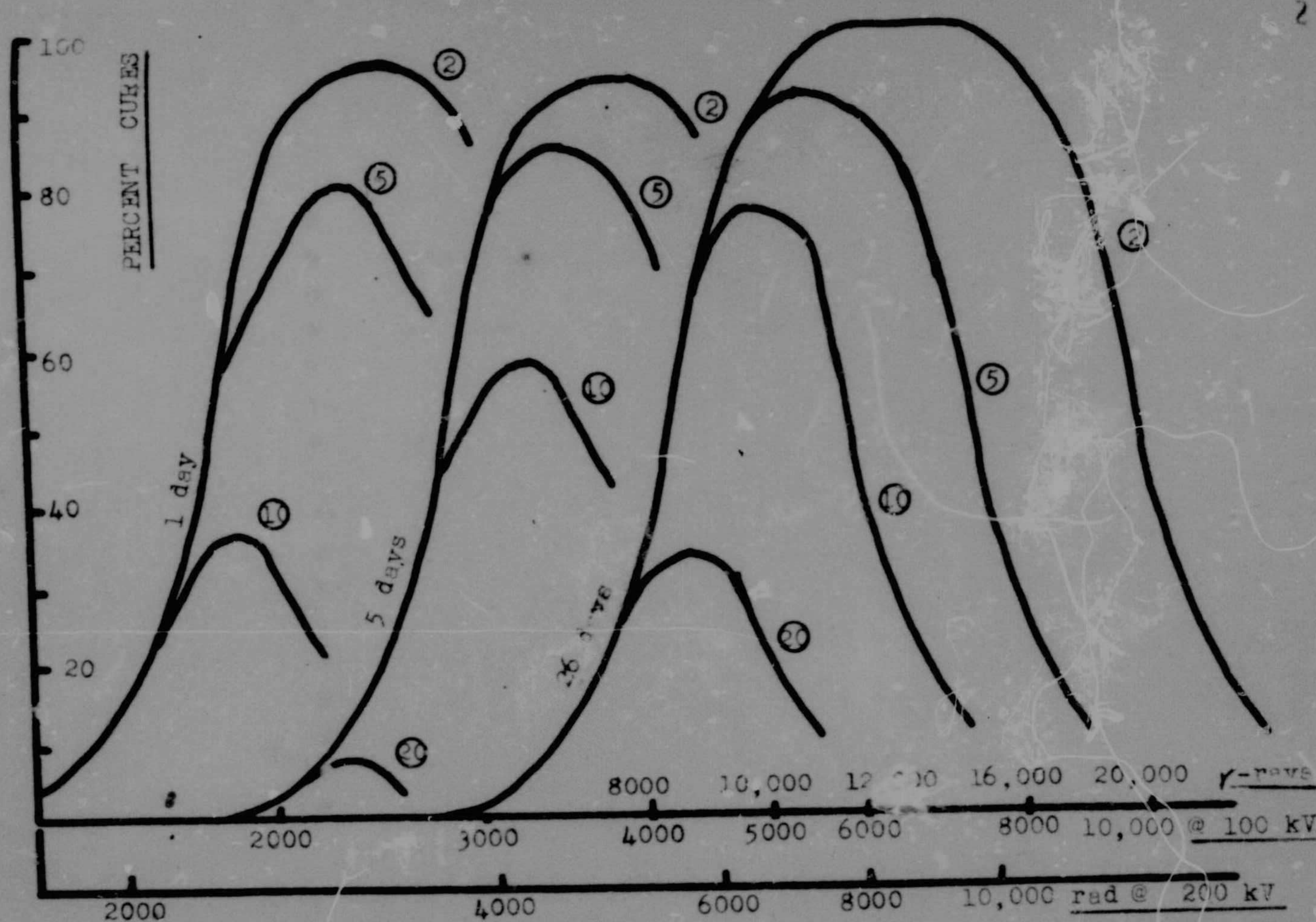


Fig. 20. Probability of cure of epidermoid cancer as a function of Dose, Time, Field-size, and Quality.

Since all the foregoing calculations give results in close conformity with established practice, it is probably justifiable to generalise the method so as to permit one to compute the optimal dose for any given clinical problem of the same type. The practical procedure by which this figure can be obtained is as follows:

(1) Physical arrangement of one or more fields giving a satisfactory percentage depth dose as in standard radiotherapeutic practice, noting the quality factor (η), the equivalent field diameter (L), and calculating from the relevant iso-doses, the heterogeneity factor (H).

(2) Selection of an approximately suitable time factor (T) as described, subject to adjustments if the therapeutic ratio is not satisfactory.

(3) Estimation of the median necrotising dose (ND-50) by substituting in the iso-effect formula the values: $\frac{4000}{\eta}\left(\frac{T}{L}\right)^{0.33}$; and the median tumour lethal dose (LD-50), using, with epidermoid cancers, the formula: $\frac{2900}{\eta}(T)^{0.22}$, and in breast cancer $\frac{1800}{\eta}(T)^{0.34}$ (data from Table I).

(4) Taking the ratio ND-50/H.LD-50 as an estimate of the therapeutic ratio (Θ/H). If this ratio does not exceed 1.5, corresponding to a prognosis bettering 90% (Fig. 19), one of the following adjustments is indicated:

- (i) changing physical factors if possible for greater homogeneity,
- (ii) reduction of field-size, if feasible, possibly using grids or sieves,
- (iii) prolongation of the over-all time by a significant factor.

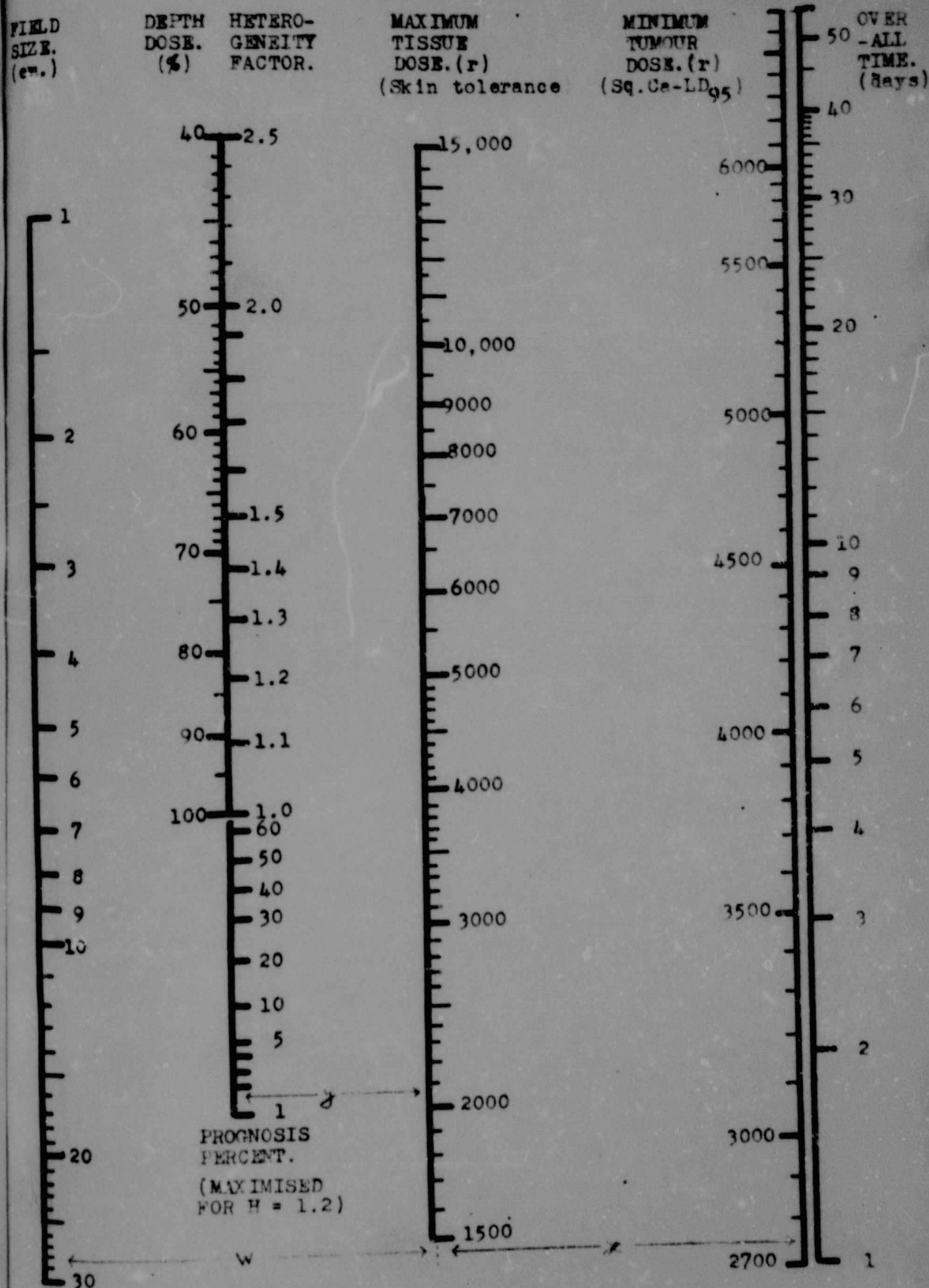
(5) Take the geometric mean between ND-50 and H.LD-50, which gives the optimum value for the <u>maximum</u> tissue dose. Alternatively, the geometric mean between ND-50/H and LD-50 gives the optimum value for the <u>minimum</u> tumour dose.

EFFECT OF TIME AND AREA FACTORS ON PROGNOSIS.

It is to some extent within the power of the radiotherapist prescribing treatment for a given tumour to vary the therapeutic ratio within certain limits by selecting the independent variates under his control. Since there is no evidence of any 'quality differential' as between tumours and normal tissues, the ratio cannot be affected by variation of quality or RBE alone. On the other hand, time and area factors can have a differential action, and the therapeutic ratio may be varied widely by selecting values for these two variates.

The therapeutic ratio and hence the prognosis depends critically on the field size. If the intrinsic radiosensitivity of a tumour is independent of the field-size, while the skin tolerance varies, as has been shown, inversely as the cube-root of the field diameter, then the therapeutic ratio must also vary according to the same function. The choice of field-size is, of course, limited by the size of the tumour to be treated (except in the case of grids with their special advantages and limitations), but in certain situations this choice may be vital. A good example is the common situation with an early Stage II cancer of the uterine cervix. If, "to be on the safe side", it is treated with radium and rontgen rays as a Stage III, irradiating the 10 cm volume thus required instead of the 5 cm field covered by the radium alone in Stage I, the therapeutic ratio is reduced by a factor of $\sqrt[3]{2}$, or 25%. This could drop the probability of cure from an optimum of 80% ($\theta/H = 1.4$) to only 25% ($\theta/H = 1.1$, see Fig. 20).

Control of the time factor is of course not subject to the same limitations, and a very wide choice of fractionation periods is available. Its effect, however, is relatively much smaller. In the case of squamous cancer ($n = 0.22$) compared with the surrounding normal skin ($n = 0.33$), the therapeutic ratio increases by no more than $T^{(0.33 - 0.22)}$, that is the ninth-root of the over-all time (compared with a cube-root function for the field-size factor).



RONTGEN (200 kV) DOSAGE NOMOGRAM.

In other words it would require an 8-fold increase in the time to raise the ratio by 25% in order to compensate for the two-fold increase in field-size with example described above. Extremely long protraction may therefore be indicated with certain large or recalcitrant tumours. In practice, it is only with 'permanent' implants or moderately long-lived isotopes that protraction is sufficiently prolonged to give a significantly improved cure rate attributable to this factor alone.

CLINICAL DOSAGE NOMOGRAMS.

In the case of squamous cell carcinoma treated radically, that is with the object of achieving the highest practicable cure-rate, the arithmetical procedure described in the foregoing section can be facilitated by using the 3 nomograms to be described below.

The first diagram (Fig. 21) is designed for use with conventional 200 kV rontgen rays delivered in equal daily fractions. The Time and Field-size scales are simple logarithmic scales equal in magnitude and can be taken as the standard cycle. It is then possible to multiply two factors each raised to a specified power by placing intermediate scales at particular distances from each of the reference scales. For skin tolerance these distances (x and w in Fig. 21) are equal since n = q = 0.33. The scale is larger than the standard by a factor of $\frac{1}{2}$ x 1/0.33 = 1.5, and the cycle commences (intersects the line joining 1 day with 1 cm) at 2000 (that is E/η for skin tolerance). The Tumour Dose scale is not central, for n ≠ q, but, since q = 0 it should overlie the time scale. To avoid confusion they have been drawn a short distance apart, which does not introduce any serious error. This scale is enlarged by a factor equal to the reciprocal of 0.22, that is 4.5; and its origin is at 2700 r (the LD-98 for squamous cancer given η = 1.5). Now if the Heterogeneity scale is a function of the therapeutic ratio and has to indicate the ratio of skin tolerance to cancerocidal dose, it follows from the geometry of the figure, that its position must be such that $\frac{y}{x + y} = \frac{1.5}{4.5}$; and the scale enlargement factor must be $\frac{x + y}{x}$ = 1.5 times that of the skin tolerance scale, In other words it would require an 8-fold increase in the time to raise the ratio by 25% in order to compensate for the two-fold increase in field-size with example described above. Extremely long protraction may therefore be indicated with certain large or recalcitrant tumours. In practice, it is only with 'permanent' implants or moderately long-lived isotopes that protraction is sufficiently prolonged to give a significantly improved cure rate attributable to this factor alone.

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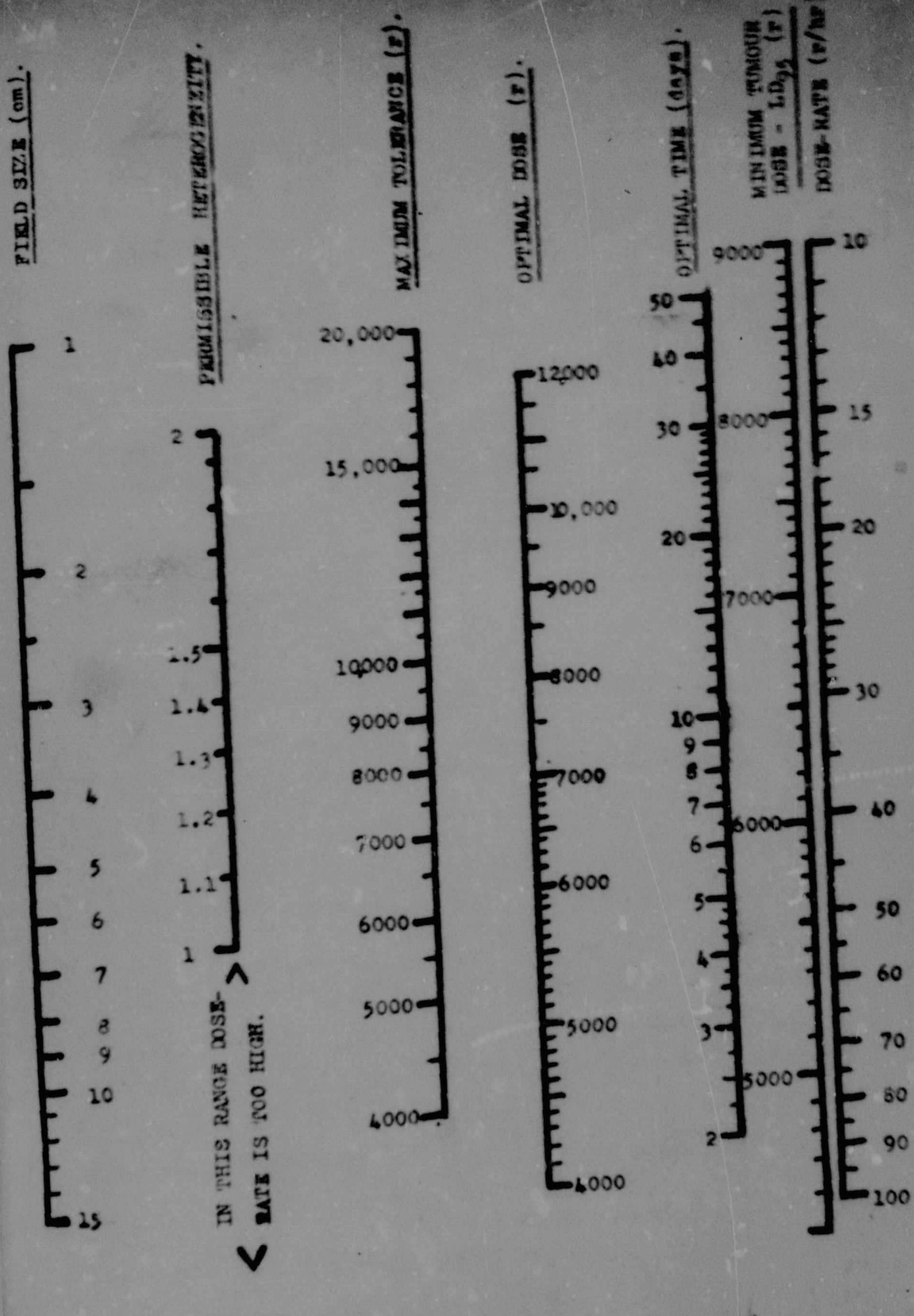
The first diagram (Fig. 21) is designed for use with conventional 200 kV rontgen rays delivered in equal daily fractions. The Time and Field-size scales are simple logarithmic scales equal in magnitude and can be taken as the standard cycle. It is then possible to multiply two factors each raised to a specified power by placing intermediate scales at particular distances from each of the reference scales. For skin tolerance these distances (x and w in Fig. 21) are equal since n = q = 0.33. The scale is larger than the standard by a factor of $\frac{1}{2}$ x 1/0.33 = 1.5, and the cycle commences (intersects the line joining 1 day with 1 cm) at 2000 (that is E/η for skin tolerance). The Tumour Dose scale is not central, for n $\neq$ q, but, since q = 0 it should overlie the time scale. To avoid confusion they have been drawn a short distance apart, which does not introduce any serious error. This scale is enlarged by a factor equal to the reciprocal of 0.22, that is 4.5; and its origin is at 2700 r (the LD-98 for squamous cancer given η = 1.5). Now if the Heterogeneity scale is a function of the therapeutic ratio and has to indicate the ratio of skin tolerance to cancerocidal dose, it follows from the geometry of the figure, that its position must be such that $\frac{y}{x + y} = \frac{1.5}{4.5}$; and the scale enlargement factor must be $\frac{X + Y}{X}$ = 1.5 times that of the skin tolerance scale,



RADIUM (ISOTOPE) DOSAGE NOMOGRAM.

Fig 22

and at the same time be $y/x = \frac{1}{2}$ times that of the tumour dose scale. These conditions are satisfied if $y = \frac{1}{2}x$, the length of the cycle is 2.25 times the standard, and its origin is placed at the point where all lines joining the same figures in the two dosage scales converge.

A single line passing through the diagram gives related values on all the scales simultaneously. Thus if a rule is set on the field-size suitable or a given lesion, and on the heterogeneity factor appropriate to the conditions of treatment, it will intersect the time scale at a point indicating the most suitable over-all time, and the two dose scales at points indicating the skin tolerance and tumour lethal doses for the conditions used. If all five scales cannot be intersected, as happens with large fields or short treatment times, the proposed treatment is unsuitable for the case in question.

The second nomogram (Fig. 22) is designed for continuous irradiation with hard γ-rays (η = 1.00) such as would obtain with radium applicators and implants or with isotopes of similar quality having half-lives long enough to ensure that no significant reduction in dose-rate occurs during the exposure period (Co-60, Ta-182). With softer radiations (Ir-192, Cr-51, I-131) a correction for RBE might be required. Here again a single line across the diagram gives all the related factors simultaneously. The Dose-Rate and Optimal-Dose scales are computed for optimal doses <u>averaged</u> over the irradiated region, and is thus compatible with the Paterson-Parker system of radium dosage tables. If the radium or isotope is correctly distributed, the corresponding maxima and minima, which depend on the heterogeneity factor, will fall within practicable limits.

The third nomogram (Fig. 23) is applicable to 'permanent' implants of radioactive sources, where the time-factor is determined by the disintegration rate of the isotope chosen. The technical factors underlying this choice, and the theoretical basis for the dosage data used in constructing this diagram have been described elsewhere (* 42).