effect on the biological response. For this reason, a high-energy RBE standard has been proposed (* 41). Furthermore, the dose-rate is not critical provided intensely pulsed sources are avoided. It has, accordingly, been accepted in many centres today (* 23) that the best standard of comparison is afforded by the $\gamma$-rays from radium, or similarly energetic photons emitted continuously with an ion-density of 10 ions/$\mu$ (LET = 0.3 MeV/$\mu$).

Whichever standard is preferred, the data summarised in Table II permits a very accurate comparison between them. In this and the following chapters we shall, for the reasons given, accept the 'radium' standard (10 ions, or 0.3 MeV, per micron), as the standard of reference taking $\eta_\gamma = 1.0$. On this basis, $\eta = 1$ for rontgen or $\gamma$-rays over 1 MeV in energy, including the photon and electron beams from non-pulsed or low-frequency ( 1 kc/s) megavoltage apparatus; $\eta = 1.4$ for 200 kV rontgen rays with Cu filtration; and has greater values for lower exciting voltages and lighter filters up to a value of $\eta = 3$ for the softest low-energy photons. Only with the heavily ionising positive particles may a biological efficiency greater than 3 be encountered, though, as has been shown, this is by no means a well-established datum (Fig. 3).

It is of interest to note that energetic $\beta$-rays from systemically administered isotopes (such as the 1.4 MeV $\beta$-ray from Na-24) (* 166), give results virtually identical with those for external $\gamma$-ray beams at equivalent integral dosage, and may be used with equal validity for RBE comparisons. Mixed gamma-radiations emanating from atomic bomb explosions have also been shown to give comparable results (* 48).

The ratios between the two standard quality levels are given in Table II, illustrating the consistency of this type of comparison

# TABLE II

RELATIVE BIOLOGICAL EFFICIENCIES OF 200 KV RONTGEN RAYS COMPARED WITH 'MEGAVOLTAGE' RADIATIONS

| HIGH-ENERGY SOURCE | TEST OBJECT | (200 kV/MeV) | REFERENCE |
|---|---|---|---|
| 30 MeV betatron | Various | 1.3 | Mitchell |
| 23 MeV betatron | Chromosomes | 1.37 | Arneson |
| " | Rabbit skin | 1.5 | Haas |
| " | Mouse whole body | 1.5 | Ting |
| " | Mouse carcinoma | 1.2 | Ting |
| 20 MeV betatron | Mouse hair greying | 1.4 | Chase |
| " | Chromosomes | 1.46 | Arneson |
| " | Mouse whole body | 1.4 | Quastler |
| " | Drosophila eggs | 1.4 | Luce |
| 17 MeV betatron | Mouse hair greying | 1.6 | Austin |
| 4 MeV linear acc. | Various | 1.3 | Paterson |
| Na-24 $\beta$-rays | Mouse whole body | 1.4 | Snyder |
| Co-60 $\gamma$-rays | Mouse whole body | 1.4 | Upton |
| Co-60 $\gamma$-rays | HeLa tissue culture | 1.3 | Bonte |
| Radium $\gamma$-rays | Mouse sarcoma | 1.5 | Sugiura |
| " | Drosophila pupae | 1.26 | Muller |
| " | Chick embryo | 1.6 | Lea |
| " | Chick fibroblasts | 1.5 | Lasnitzki |
| " | Mouse tail skin | 1.5 | Mottram |
| " | Mouse whole body | 1.3 | Storer |
| " | Human skin erythema | 1.6 | Quimby |
| " | Human skin reaction | 1.5 | Cohen |
| " | Skin tolerance | 1.6 | Andrews |
| " | Human oral cancer | 1.4 | Wood |
| 1000 kVp X-rays | Mouse testis | 1.3 | Kohn |
| " | Human skin reaction | 1.3 | Stone |
| | MEAN | = 1.403 | (±.024) |

in various mammalian tissues, and supplying an accurate estimate of the quality parameter in this clinically important range. The RBE for 'conventional' rontgen radiation, compared with the 'megavoltage' standard, that is the value of $\eta = 1.40$ for the 200-250 kV deep-therapy range, is perhaps the most firmly established, certainly the most thoroughly tested, RBE datum in clinical radiobiology, and can be applied without reservation both in the iso-effect formula and in clinical dosimetry in general. For this reason the two corresponding sets of parameters are given in Table I.

## RBE IN DEEP SEATED TISSUES.

As shown previously, quality changes in depth in the transmitted beam are also likely to modify the RBE insofar as it affects deep-seated tumours and tissues. As a result of this effect, it follows that the factors obtaining in Fig. 4 are strictly applicable only to relatively superficial tissues. With megavoltage quality photons, for example, there is already a perceptible softening, and a significant increase in RBE ($\eta > 1.1$) at a depth of 5 cm; while at 10 cm., the average quality of the beam approaches that of conventional 200 kV rontgen rays ($\eta = 1.4$) (* 28). This phenomenon combining the skin-sparing effect of the high-energy incident beam with the greater efficacy of the softer radiation in depth, is a most propitious and advantageous circumstance, which will obviously have to be taken into account in assessing optimal dosage for deep-seated tumours treated by means of megavoltage radiations.

Although published data on the quality-change in depth are scanty, the general trend is sufficiently consistent to permit construction of the composition graph in Fig. 5 based on measurements by Clarkson and Maynard (* 36), Stenstron and Marvin (* 169), Greenfield (* 76), and Bonte et al. (* 28). Fitting the 5 curves to a common depth scale, one obtains the

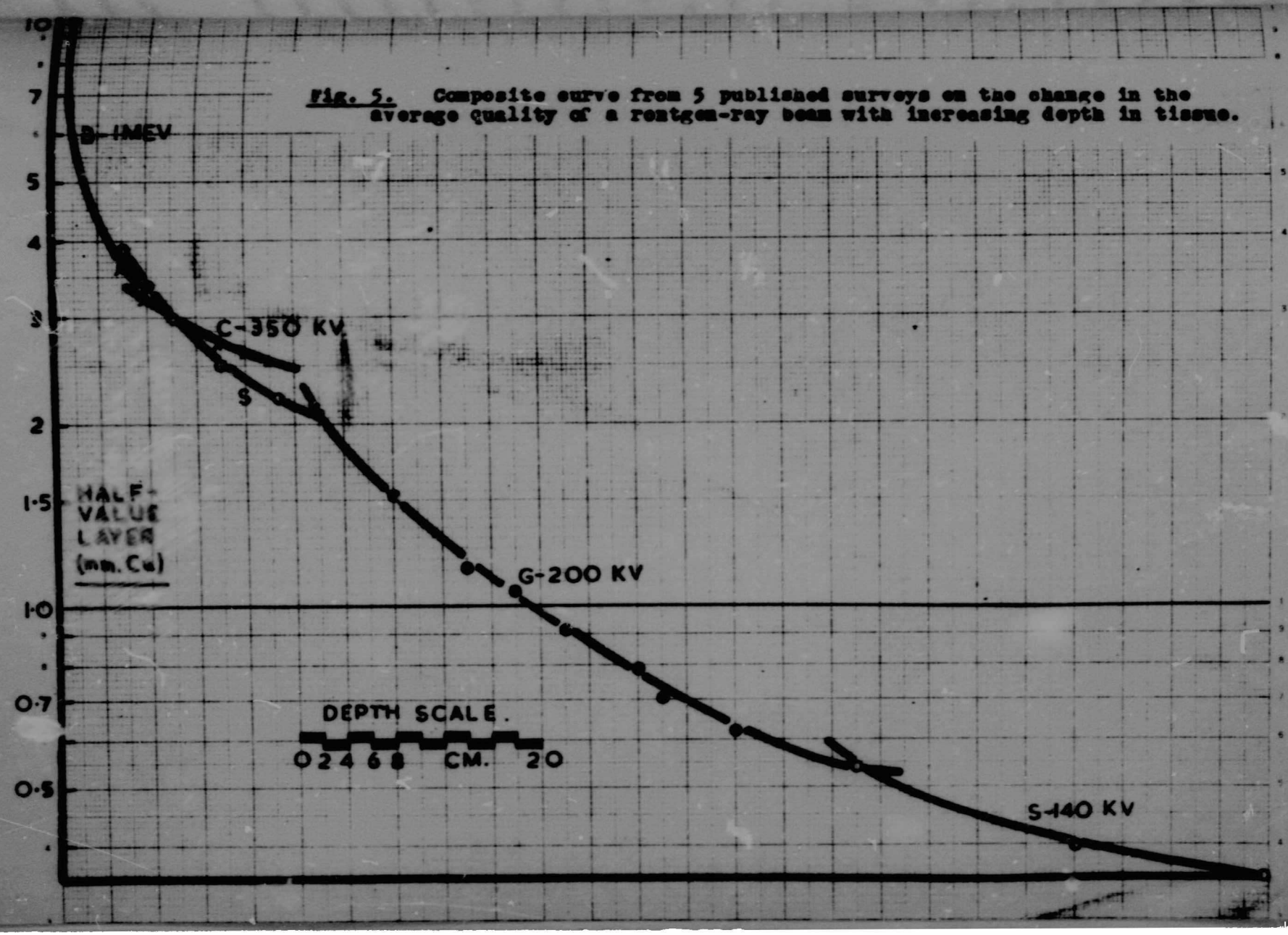



Fig. 5. Composite curve from 5 published surveys on the change in the average quality of a rontgen-ray beam with increasing depth in tissue.

chart here tentively presented as a working proposition for clinical use. Given the half-value layer of the incident beam, one can, using Fig. 5, determine the quality of the radiation reaching any particular depth. Then referring to Fig. 4 the RBE appropriate to the radiation reaching tissues at the point of interest may be estimated in terms of '$\eta$' and the factor $a = \frac{1}{\eta}(2,02)$ is thus readily obtained for inclusion in the iso-effect formula (1,01).

## SUMMARY OF CHAPTER III

The quality factor, as assessed by the half-value layer, kilovoltage, average wavelength, or rate of linear energy transfer (LET) is considered in relation to the relative biological efficiency (RBE) for animal and human tissues of various types of radiation. By simple graphical interpolation, the RBE-factors required for incorporation into the iso-effect formula are derived, and shown to be valid at least in the range of clinical interest. Taking $\eta = 1.00$ for radium $\gamma$-rays and megavoltage radiations, its value is shown to be 1.403 ($\pm$ .024) for orthovoltage rontgen rays, and approaches a factor of 3 in the superficial therapy range.

## CHAPTER IV. THE TIME FACTOR.

### THE RECIPROCITY LAW AND RECOVERY FUNCTIONS.

Chemical and biological effects of ionising radiation are, in general, of two types according to whether or not the process is reversible. In wholly irreversible reactions, the so-called 'reciprocity law' of Bunsen and Roscoe (* 29) holds good. This law implies that, for an effect of a given magnitude, the product of intensity (I) and time (T) is constant, that is

$$I.T = k \qquad (2, 03)$$

For photographic effects this function is expressed in the form: "equal products of intensity and time produce equal degrees of blackening in the developed photographic emulsion". In the biological field the reciprocity law seems to apply only in the case of certain genetic effects of radiation, which appear to be fully cumulative irrespective of the duration of exposure.

Many chemical systems will show some 'reciprocity law failure' at both extremes of the range of radiation intensities available. In particular, they will exhibit a diminished effect at very low dose-rates suggesting some degree of 'recovery' on the part of the irradiated material. In the case of extremely prolonged photographic exposures at very low levels of illumination, this effect is described by Schwartzschild's law (* 163)

$$I.T^{m} = k \qquad (2, 04)$$

where 'm' is a positive fraction. This type of empirical 'power function' has also been found to apply in many physical, chemical and biological 'recovery' systems (* 136).

With the exception of the special genetic effects mentioned, almost all biological objects exposed to ionising radiation exhibit a more-or-less marked reciprocity law failure. In fact recent studies

of radiation-induced mutations in mammals, in contradistinction to such tissues as Drosophila sperm commonly used in genetic research, have revealed significant dose-rate effects even in the genetic material (* 158). These departures from the reciprocity law are indicative of some degree of recovery from the effects of irradiation. This is manifest by the marked dependence of the effective level of dosage on treatment time. A given physical quantity of radiation will give a smaller effect if it is spread over a relatively long time, than if the same dose were delivered in a shorter period. Similarly, in order to produce a given result with a protracted course of radiation, one requires a substantially larger dose that that found to be effective in a short exposure. An analysis of the dose: time relationship for human tissues by Strandqvist (* 173) indicated that the total given dose (D) is related to the over-all treatment time (T) by the parabolic function

$$D = k.T^n \qquad (2, 05)$$

where 'n' is a positive fraction. There is an obvious correspondence between the Schwartzschild and Strandqvist functions, since $D = \bar{I}.T$, in which case it can be shown that $n = 1 - m$.

If this empirical function proves to give a consistently good description of the clinical dose: time dependence, and if more accurate data on the magnitude of the exponent 'n' can be obtained for the whole range of tissues and tumours irradiated, then the factor '$T^n$' can be taken as an estimate of the magnitude of the time-factor and substituted for the factor 'b' in the clinical iso-effect formula (1, 01).

Before any such simple function can be applied with confidence, however, it becomes necessary to consider the following four timing variables: namely, the intensity or dose-rate of the irradiation; whether the exposure is continuous or intermittent; and, in the latter

case, the manner of fractionation, that is the size, frequency and spacing of individual doses; and finally, the over-all time of the whole irradiation procedure. If it is found that any of these variables affect the dose-dependence to a different degree in various tissues and tumours, then some selective action or advantageous differential effect of radiation could be exploited in clinical radiotherapy by a judicious choice of time factors. In this regard, the over-all treatment time has been shown to be the most significant factor, and a large volume of accurate observation is available for assessing its significance. On the other hand, the dose-rate and the manner of fractionation appear to be relatively unimportant. Insofar as a differential action between tissues can be exploited clinically, the recovery rate of epidermoid cancer, in particular, is significantly less than that of normal human skin, so that prolongation of a course of clinical radiotherapy can, in this instance, have very material advantages.

VARIATION IN DOSE-RATES.

Within the limits usually encountered in practice, and considered apart from associated changes in over-all time, this factor appears to have a quite insignificant effect upon the intensity of the reaction. In certain cytological studies, such as chromosome interchanges, where the final result may be influenced by the duration of treatment in relation to the mitotic cycle, the degree of injury is significantly smaller at low dosage-rates (* 175). In the absence of synchronous cell-division, however, this type of effect seems unlikely to appear in complex multicellular organisms and their tissues.

At exceedingly great intensities, however, as with betatrons or similar apparatus giving pulsed outputs with instantaneous dose-rates of some millions of rad per second, the high local ion-densities

and consequent increase in apparent RBE, will result in stronger biological reactions (* 78). At the other extreme, with very low intensities of the order of one rad per minute, the time required to deliver any substantial dosage is necessarily so prolonged that the effect of the extended over-all time cannot be distinguished from that of low dose-rate per se.

Excluding these extremes, studies on the human skin erythema reaction have shown no perceptible difference attributable to changes in dose-rate over the whole range between 10 and 10,000 rad/min (* 32, 110). In one significant experiment where the over-all time was kept constant, McWhirter (* 122) showed that the intensity of the erythema produced by 2000 r of radium γ-rays, in 7 equal daily fractions of 286 r, [illegible] whether the radiation was given at 12 r/hr. or at 1200 [illegible] response of skin cancer was also identical at the two intensities. The reaction given by medium-voltage rontgen rays, similarly fractionated, was also the same at all intensities between 3.3 and 360 r/min.

However, Kepp's analysis (* 101) of the effects of intensity upon the effective erythema dose shows that the foregoing conclusions have limited validity. It would seem that the reaction is independent of dose-rate if a large number of fractions (about twelve) are used (* 103). With single doses, greater effects are obtained with greater intensities, and Saltzman's results (* 90) in this connection are confirmed. Inspection of these figures shows that the effective dose varies inversely as the fifth-root of the intensity for a single session and that this variation diminishes rapidly as the number of fractions are increased. With the range of intensities generally used in therapy, therefore, the reactions are in fact largely independent of dosage-rate.

INTERRUPTION OF EXPOSURE.

Differences between the effects of continuous protracted irradiation

and intermittent exposure at sufficiently frequent intervals (say not more than one day) over the same total period, would also appear to be insignificant. In McWhirter's (* 122) experiment on dose-rate effects, the lower range on intensity in radium exposure amounted to a continuous treatment over 7 days, which did not differ in effect from the same total dose delivered in seven equal daily fractions.

MANNER OF FRACTIONATION.

Variations in the fractionation scheme have, in general, a relatively slight effect upon biological reaction, compared with the over-riding importance of the over-all time in this regard. There is, however, strong indirect evidence that an effect attributable to this factor as distinct from the over-all time does in fact exist, and may indeed significantly influence the outcome in some clinical irradiation procedures. Comparative data are rather meager. Most of the available information on dose-time interactions is based upon the reactions of patients treated by equal daily fractions, usually on 5 or 6 days a week, for some weeks. Another substantial group of patients have received continuous radium treatments over shorter periods, seldom longer than 7 days in duration. However, these two modalities, at least in routine clinical usage, differ in so many other respects, including HVL, field-size, depth-dose gradients, dose-rate and over-all duration, as to preclude any valid comparisons upon the effects of the fractionation procedure per se.

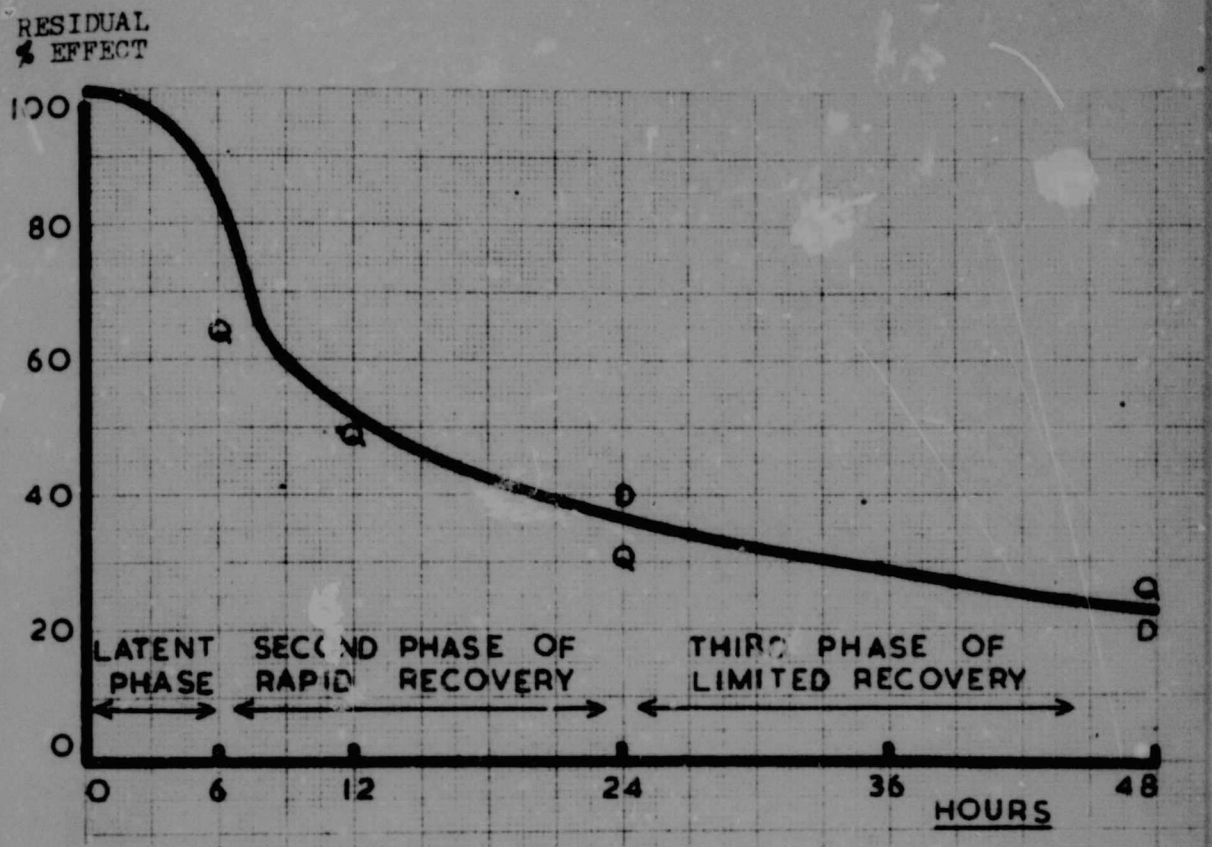
There is, on the other hand, a small amount of information bearing upon the problem from studies on the recovery of human skin from the first, and from subsequent doses of radiation given at various intervals, as assessed by the erythema reaction produced with particular fractionation schemes. From the data originally reported by Duffy (* 51), and by Quimby and MacComb (* 150) on the TED for 2 equal fractions given at various intervals ranging from 6 to 96 hours apart, one can estimate the degree of initial recovery as a function of time. A composite

recovery curve derived from these results is given in Fig. 6a. More recent investigations by Kepp (* 102), and by Du Sault (* 52), would seem to confirm the validity of this curve, at least insofar as its general shape is concerned.

Among the significant features of the 'initial recovery' curve of human skin are 3 distinct phases: Firstly, there is a latent interval of 5 to 6 hours before any recovery commences, and any treatments given within such a short period appear to be fully cumulative no matter how fractionated. A treatment time of under 5 hours could therefore be considered a 'single short exposure' such as that discussed previously. After this period, there is a more-or-less rapid depreciation in residual effect for about 48 hours, after which the curve gradually merges with the third phase of rather slow recovery with partial cumulation over long periods.

Further information on this score is available through comparison of reactions in the case of standard daily fractionation procedures with those in clinical experiments in which the course of radiation is fractionated at intervals other than one day. As shown by Van Rooijen (* 136), there is evidence of a favourable differential effect between skin and epidermoid cancer when this tumour is irradiated twice daily. Under these conditions, the skin is reported to tolerate a dose of radiation, delivered in 10 fractions over 5 days, almost equal to the tolerance dose for 30 daily fractions. The tumour, on the other hand, reacts much more vigorously and completely to the former procedure.

Longer intervals between treatments, such as 'alternate day' or 'twice weekly' fractionation procedures, appear to give a favourable differential action in the therapy of breast cancer (* 40), but not with epidermoid cancer (* 160). There is also some evidence for a critical interval between treatments at which differential effects are optimal (* 52).



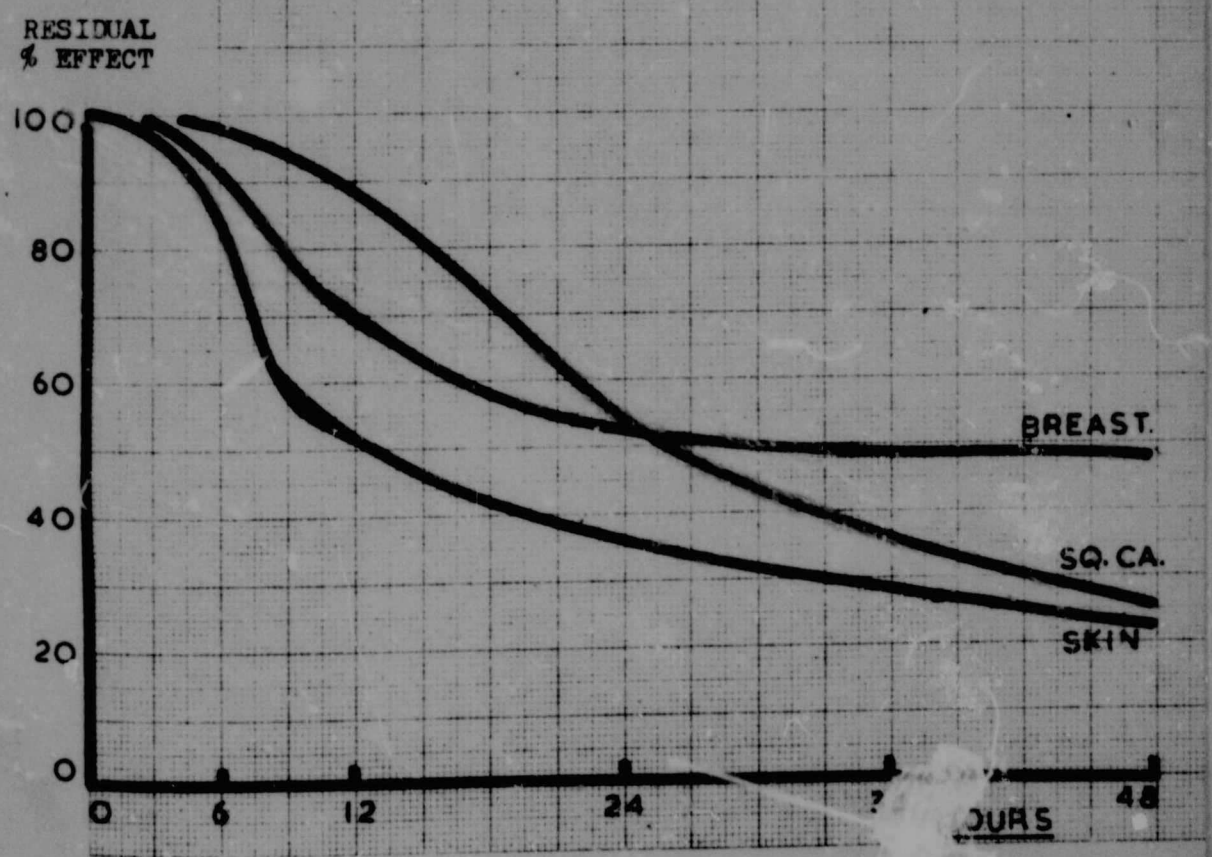




Fig. 6. (a) Initial recovery curve of human skin as assessed upto 48 hours after a single exposure.

(b) Three possible variations in shape of the initial recovery curve, which could account for observed differences in effect associated with different fractionation procedures in certain tumours.

While it is not yet possible in the present state of knowledge to express these relations in a precise quantitative formula, the observed differential effects could be explained by differences in the initial phases of the recovery curves for the tumours and tissues concerned, as suggested in Fig. 6b. These curves are designed to show how a maximum differential could appear between skin and squamous cancer at 12 hours, and between skin and breast cancer at 48 hours to account for observed responses as reported by Van Rooijen (* 186) and by Ambrook (* 160) respectively; and yet retain all the general features of the triphasic initial skin recovery curves described in Fig. 6a.

**OVER-ALL TIME.**

The most important of all the time variables, at least in clinical practice, is the total treatment time. In assessing its effect upon the quantity of radiation required to produce a given reaction, the manner of fractionation can usually be disregarded without significant loss of accuracy. In clinical radiation therapy it is usually required to assess separately the recovery function of the skin, which is necessarily irradiated in almost every therapeutic procedure, as well as that of the particular tumour concerned.

In the case of normal human skin, a large volume of data concerning its recovery is available for two levels of reaction - the 'threshold erythema' or first degree reaction; and the 'skin tolerance', usually implying the third-degree or exudative reaction. The former is amenable to more accurate and objective measurement, but the latter is of far greater practical importance in determining clinical dosage. However, the over-all recovery factor, that is, the factor by which a given single-shot dose has to be increased in order to produce, with a more-or-less prolonged course of treatment, the same effect as that given by a single exposure, appears to be almost the same at both levels of reaction.

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The available literature on the recovery function of human skin is collected and analysed in Table III. Inspection of the data shows the very considerable increase in dosage tolerated with longer treatment times. This relationship is more clearly illustrated by plotting the data graphically on logarithmic co-ordinates (Fig. 7), from which it will be seen that almost the whole range of clinical observation and experiment on this problem from many different centres, can be fitted satisfactorily by very similar straight lines. Such lines correspond to parabolic functions of the type $D = k.T^n$, described previously (3, 05), where 'n' is given by the slope of the line. This analysis thus confirms the validity of the Strandqvist type of power-function, and enables one to estimate the magnitude of the recovery exponent 'n' from the observed slope of the line as fitted by eye, or by the algebraic methods to be described. More rigorous statistical methods using 'least-squares regression equations' could also be used for estimating the parameters from the observed reactions and dosage factors on numbers of individual cases collected into a single body of comparative data. With the variety of observations shown in Table III however, the graphical methods seem to be adequate though they do not readily permit assessment of the variance of estimated parameters, and hence give no information on the degree of confidence that can be placed upon such estimates.

The best available estimates of the recovery parameter for normal human skin obtainable from all the data in Table III by regression analysis or from the graphical method illustrated in Fig. 7 appears to be $n = 0.34$ for the threshold erythema reaction, and $n = 0.33$ for the skin tolerance dose. If these estimates are assumed to measure the same population, we could probably accept $n = 0.33$ as a convenient working standard. The estimate of the same parameter through a rigorous statistical analysis of 150 observed reactions in radiotherapy

## TABLE III. TIME-FACTOR DATA

a) Initial Recuperation of Human Skin (Effect of 2 spaced fractions, after Quimby and MacComb, 1936).

| INTERVAL (hours) | ERYTHEMA DOSE (total r in air) | % | Percent Residual Effect at 2nd Exp. |
|---|---|---|---|
| 0 | 525 | 100 | 100 |
| 6 | 640 | 122 | 64 |
| 12 | 700 | 133 | 50 |
| 24 | 800 | 152 | 31 |
| 48 | 850 | 162 | 24 |
| 96 | 880 | 168 | 19 |

b) Time-Dose Relationship for the Threshold Erythema Reaction

| DAILY FRACTIONS. | ERYTHEMA DOSE (after Quimby). | TIME FACTOR | ERYTHEMA DOSE (after Reisner). | TIME FACTOR |
|---|---|---|---|---|
| 1 | 525 | 1.00 | 1000 | 1.00 |
| 2 | 800 | 1.52 | 1300 | 1.30 |
| 3 | 825 | 1.57 | 1500 | 1.50 |
| 4 | - | - | 1600 | 1.60 |
| 5 | 925 | 1.76 | - | - |
| 7 | - | - | 2100 | 2.10 |
| 12 | 1200 | 2.28 | 2400 | 2.40 |
| 27 | - | - | 2700 | 2270 |

c) Clinical 'Tolerance' Dosage Tables (after Ellis, Jolles & Mitchell, and Paterson).

| TIME* W - D | FIELD-SIZE (Ellis' Data) 6x4 | 8x6 | 10x8 | 15x10 | 20x15 | TIME FACTOR. | FIELD-SIZE (Jolles' Data) 8x6 | 10 ø | 15x10 | 20x15 | TIME FACTOR. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 - 1 | 2000 | 1750 | 1450 | 1250 | 1100 | 1.00 | 1750 | 1540 | 1450 | 1300 | 1.00 |
| 1 - 5 | 3000 | 2600 | 2200 | 1900 | 1700 | 1.52 | 3460 | 3050 | 2850 | 2550 | 1.96 |
| 2 - 12 | 4400 | 4000 | 3300 | 2850 | 2650 | 2.29 | 4580 | 4050 | 3800 | 3400 | 2.62 |
| 3 - 19 | 5000 | 4500 | 3750 | 3300 | 2900 | 2.59 | 5200 | 4600 | 4300 | 3850 | 2.96 |
| 4 - 26 | 5500 | 5000 | 4100 | 3650 | 3200 | 2.83 | 5500 | 4850 | 4550 | 4050 | 3.12 |
| 5 - 33 | 5800 | 5250 | 4350 | 3850 | 3350 | 3.01 | 5660 | 5000 | 4700 | 4175 | 3.21 |
| 6 - 40 | 6000 | 5500 | 4500 | 4000 | 3500 | 3.13 | 5750 | 5075 | 4750 | 4250 | 3.28 |
| AREA FACTOR | 1.38 | 1.21 | 1.00 | 0.86 | 0.76 | | 1.14 | 1.00 | 0.94 | 0.85 | |

| TIME (D) | FIELD-SIZE (Paterson's Data) 6x4 10x4 | 8x6 15x4 | 15x 5 12x10 | 15x10 20x10 | 20 ø 20x20 | TIME FACTOR |
|---|---|---|---|---|---|---|
| 1 | 2100 | 1900 | 1700 | 1500 | - | 1.00 |
| 4 | 3700 | 3400 | 2900 | 2500 | - | 1.73 |
| 8 | 4700 | 4300 | 3800 | 3300 | 2700 | 2.24 |
| 12 | 5700 | 4700 | 4100 | 3600 | 3000 | 2.43 |
| 19 | 5500 | 5100 | 4500 | 4000 | 3400 | 2.65 |
| 33 | 6300 | 5900 | 5200 | 4800 | 4300 | 3.02 |
| AREA FACTOR | 1.33 | 1.21 | 1.08 | 0.92 | 0.78 | |

* In this context 'W' is the nominal treatment time in weeks, and 'D' the actual over-all time in days.

patients by Cohen and Kerrich (* 44) gave an average value of n = 0.31 (± .026). Similar, though less rigorously established estimates, have been accepted by du Sault (* 52) and by Andrews and Coppedge (* 8).

If, as seems to be the case, 'n' is reasonably constant under various treatment conditions, that is, it is a true parameter of the tissue concerned, then '$T^n$' is an adequate estimate of the time-factor in the iso-effect equation (1, 01) and can be substituted for 'b' in that formula. Thus the time-dependence of human skin reactions, and hence of the clinical 'tolerance dose' is fairly adequately described by the formula $D = k.T^{.33}$. This could also be expressed by the following empirical rule: The dose required to produce a given skin reaction varies as the cube-root of the over-all time of exposure.

The limitations of this rule should, however, be clearly understood. Firstly, the value of 'n' may not, as has been assumed, be entirely independent of other factors. For example, there appears to be some correlation between the recovery function and the quality or RBE of the radiation (* 44), though in no instance has the estimate deviated sufficiently to preclude its clinical applicability. Further, it should be borne in mind that the parameter is valid only within the range of protraction and fractionation investigated, that is, up to 60 days; and while interpolated values within this range are reasonably well-founded, it is not always permissible to extrapolate the function to longer periods of time. It is possible that the extremely protracted irradiations given with 'permanent' deposition of certain long-lived radioactive substances may entail some revision of this estimate.

In the absence of evidence to the contrary, the same factor may, for the purposes of practical radiation therapy, be assumed to apply to the normal tissues, including mucous membranes and the connective tissue elements constituting the tumour bed in most situations. This conclusion is confirmed by du Sault's (* 52) observation showing

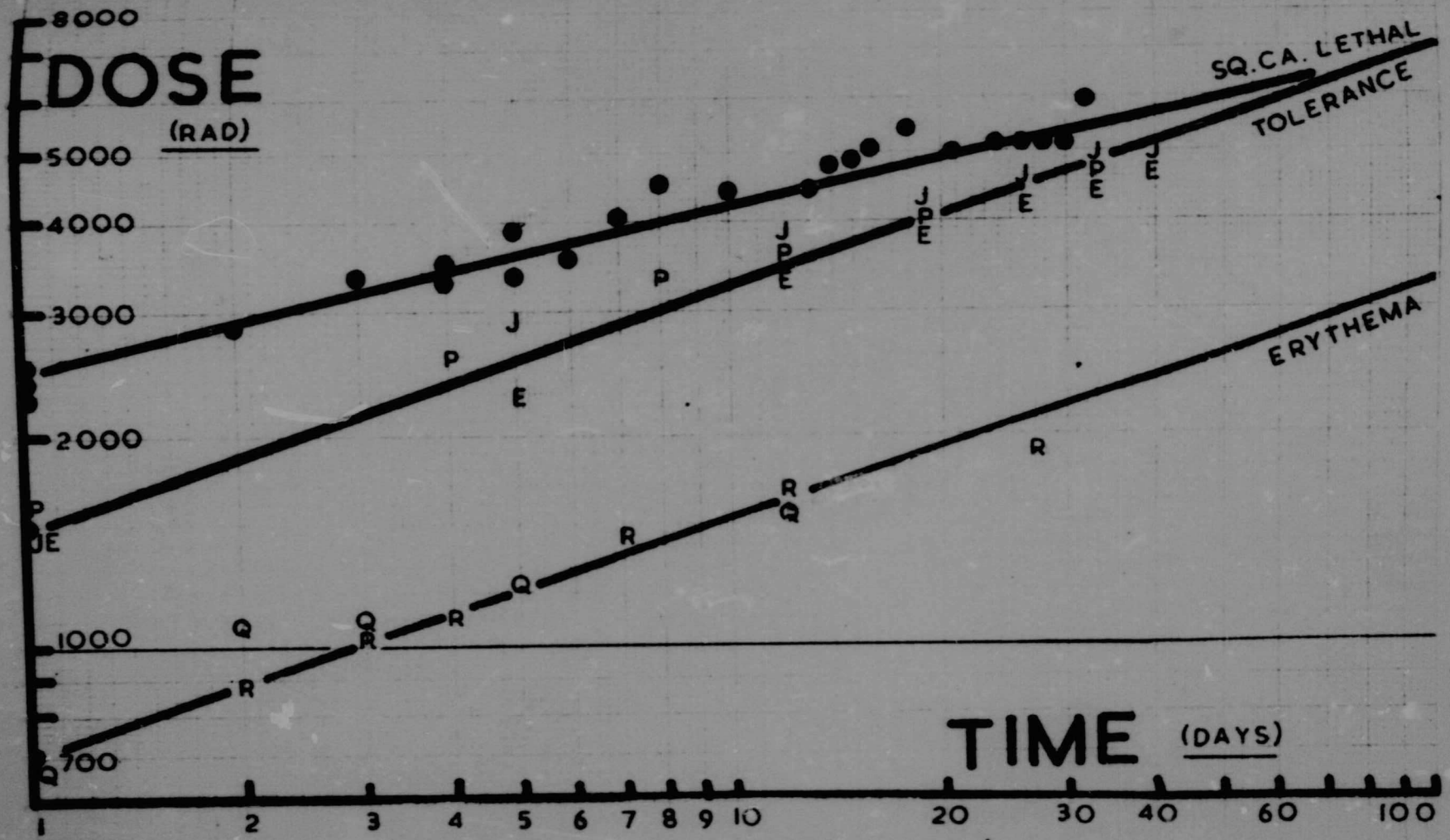


Fig. 7. Logarithmic dose-time 'iso-effect' curves for skin erythema, skin tolerance, and the cure of epidermoid cancer, fitted to published data. Note the difference in slope between the regression lines for the tumour and those of normal skin in this regard.

roughly similar recovery functions for a variety of human tissues. As shown in Table VI most human tissues have a similar time-dependency 'n' ranging between 0.2 and 0.3.

THE RECOVERY FUNCTION OF TUMOURS.

This can be assessed by similar methods to those used in the case of normal skin, though the available information is far less abundant, and rather less precise. In the case of squamous cell cancer, however, there is a fairly adequate body of data, from many independent sources, by which the recovery parameter for the tumour can be estimated and checked. With tumours the reaction level concerned, which might be, say, the ED-50, cannot be observed directly on individual cases as with skin reactions, but has to be based on an average, or rather a median, value of dosage associated with the particular cure-rate. A simple graphical solution is that used by Strandqvist (* 173) whereby 'cures' and 'failures' are plotted separately on the graph, and the best-fitting line drawn between the two groups of points.

A more accurate method is to collect a large number of estimates of the ED-50, or other similar known level of effect, for a variety of discrete over-all treatment times. It is common practice for a particular radiotherapy centre to choose a standard dose-time combination, generally around the ED-90 range, for routine use. If a large number of such dose-time combinations from many different centres can all be shown to give approximately the same cure-rates, then a satisfactory estimate of the recovery parameter can be obtained by graphical or regression methods.

With the exception of some accessible tumours, there are usually such wide differences in cure-rates in different institutions as to render this method invalid. In these cases it is possible to estimate the true ED-50 for each chosen over-all time from given data on cure-rates associated with the particular dose-time combination, if one knows,

or can safely assume, the coefficient of variation for that particular tumour. For example, a preoperative dose of 2500 rad in 3 weeks has been reported to cure breast cancer in only 20% of cases (* 120). Given a coefficient of variation for this tumour of 11% (* 40), it can be shown statistically that the actual ED-50 under the same conditions must be around 2800 rad. Using this method, the writer was able to show that satisfactory and consistent information may be extracted from extremely heterogeneous data (* 40).

The most rigorous algebraic statistical approach to this problem is through Kerrich's (* 104) adaptation of Finney's (* 61) method, as described on page 80.

RECOVERY FUNCTION OF EPIDERMOID (SQUAMOUS CELL) CARCINOMA.

The available published data on the recovery function for this tumour are tabulated in Table IV and analysed graphically in Fig. 7. From these observations the recovery parameter for epidermoid cancer appears to be n = 0.22. The analysis based upon 100 radiotherapy patients by Cohen and Kerrich (* 44) gave a value of n = 0.25 by a graphical method for minimising the variance, and of n = 0.289 (± .025) by Kerrich's method. The standard error of this estimate indicates the rather large uncertainty in our knowledge of the parameter, which might lie anywhere between 0.24 and 0.34 though other consideration to be discussed in the following section prove that its value must fall somewhere near the lower limit of this range. Estimates from Strandqvist (* 173) (skin and lip cancer, 0.22); Gancia (* 68) (cervix, 0.23); Andrews and Coppedge (* 8) (squamous carcinoma, 0.22); Nolan and du Sault (* 135) (cervix, 0.25); all seem within reasonably close agreement. For practical purposes, the best available estimate is that based upon the large number of observations collected in Table IV, from which we take our working value of n = 0.22.

or can safely assume, the coefficient of variation for that particular tumour. For example, a preoperative dose of 2500 rad in 3 weeks has been reported to cure breast cancer in only 20% of cases (* 120). Given a coefficient of variation for this tumour of 11% (* 40), it can be shown statistically that the actual LD-50 under the same conditions must be around 2800 rad. Using this method, the writer was able to show that satisfactory and consistent information may be extracted from extremely heterogeneous data (* 40).

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# TABLE IV

## RECOVERY FUNCTION OF SQUAMOUS CELL CANCER OF HUMAN SKIN

| REFERENCE | TIME (days) | DOSE (LD-90 'r') | TIME FACTOR |
|---|---|---|---|
| McWhirter, 1936. | 1 | 2500 | 1.00 |
| | 2 | 2850 | 1.14 |
| | 3 | 3300 | 1.32 |
| | 4 | 3500 | 1.40 |
| | 5 | 3900 | 1.56 |
| | 8 | 4500 | 1.80 |
| | 14 | 4800 | 1.88 |
| | 28 | 5100 | 2.04 |
| Flood and Smithers, 1939 | 1 | 2500 | 1.00 |
| | 10 | 4500 | 1.80 |
| | 15 | 5000 | 2.00 |
| Widman, 1941 | 1 | 2500 | 1.00 |
| | 5 | 3200 | 1.28 |
| Strandqvist, 1944. | 1 | 2250 | 0.90 |
| | 4 | 3400 | 1.36 |
| | 7 | 4100 | 1.64 |
| | 21 | 5000 | 2.00 |
| | 30 | 5100 | 2.02 |
| Hale and Holmes, 1947 | 1 | 2300 | 0.92 |
| | 6 | 3600 | 1.44 |
| Eberhard, 1947 | 14 | 3600 | 1.44 |
| Ivey, 1948 | 26 | 5000 | 2.00 |
| Martin and Martin, 1948 | 13 | 4500 | 1.80 |
| Paterson,, 1948 | 18 | 5500 | 2.20 |
| | 32 | 6000 | 2.40 |
| Del Regato, 1949 | 25 | 5000 | 2.00 |
| Mallender, 1950 | 1 | 2250 | 0.90 |

Regression values: $DOSE = 2500 \times T^{n}$ ; $n = 0.220$

The fact that the recovery rate of epidermoid cancer is substantially less than that for normal skin explains the clinical advantages of prolonged protraction or fractionation in the case of this tumour. The difference in magnitude of the parameter 'n' in the two instances is, therefore, a critical one, upon which the whole rationale of fractionated rontgen therapy is based. However, the estimates of parameters are necessarily subject to sampling errors, which might well effect computed optimal doses based on the assumed differences. Since the standard errors of our estimates for 'n' are approximately 10% of its mean value (* 104), the difference between the estimate of n = 0.33 for skin, and n = 0.22 for epithelioma is barely significant.

In Strandqvist's investigation no clear distinction between the tumour and normal tissue was made, so that if a real difference exists between the two tissues, application of his curve as a general correction factor for variation in treatment time would be erroneous. The existence of a real differential recovery factor in the two cases is supported by Rubenfeld's (* 157) results on a series of squamous cell carcinoma of the oral cavity treated by extrapolating the Strandqvist plot to short treatment times in the order of 1 to 3 days, and delivering the corresponding doses. The expected tumour regressions were observed, but the skin and mucosal reactions were uniformly excessive. This result indicates that Strandqvist's estimate of the recovery function is applicable to the tumour, but not to normal skin and mucosa, and that the latter must have a greater recovery potential than the former. Thus, although the magnitudes of the two parameters are not well-determined, clinical observation proves that the difference between them is a real one, and a true differential recovery must exist.

RECOVERY FUNCTION OF HUMAN ADENOCARCINOMA.

In the case of human mammary cancer, the relevant literature has been summarised by Cohen (* 40), whose data are here reproduced in

Table V, and analysed graphically in Fig. 8. Firstly an analysis of 60 patients treated in the Johannesburg Hospital with a variety of dose-time techniques prior to the adoption of the standard or optimal procedure in that institution was made. This showed that the median lethal dose for the tumour was 1270 r (single exposure at 200 kV) and that the recovery exponent was of the order n = 0.35. Both these parameters were also estimated from the published data by an independent method providing a valuable check on the accuracy of our Departmental estimates. For this purpose, reference was made to all available published observations on the radiotherapy of breast cancer. The majority of the relevant papers on the subject however, had to be discarded for the purpose of this analysis on account of insufficient technical information. In many cases the dosage was not given, or given in such a way (air doses, without specifying the size, number and position of the portals) that the tumour dose could not be estimated. In others either the overall time nor the size of the daily dose was available. There remained the 19 publications listed in Table V from which relevant data could be extracted.

In Table V the minimum tumour doses (calculated) and the number of fractions (usually daily) are listed together with the proportion of cases cured by that particular combination of treatment factors. With pre-operative irradiation this cure rate is generally given by the author and is usually based on histological examination of the surgical specimens. With post-operative irradiation one can estimate the cure rate actually ascribable to the radiation by comparing the local recurrence rates in irradiated and unirradiated groups in the same series. Thus, if the cure rate following surgery alone is $C_s$, and that given by surgery plus radiation is $C_{sr}$, then the probable proportion of cures given by the radiation alone $C_r = (C_{sr} - C_s)/(1 - C_s)$. For example, Pendergrass (# 144) showed that surgery alone gave 22 per cent. five year cures ($C_s = 0.22$), while in

**Author** Cohen L
**Name of thesis** Radiation Parameters 1960

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