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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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PHYSICAL AND BIOLOGICAL PARAMETERS AFFECTING THE REACTION OF HUMAN TISSUES AND TUMOURS TO IONIZING RADIATION

A STATISTICAL AND EXPERIMENTAL STUDY ON THE DEVELOPMENT OF METHODS FOR DETERMINING THERAPEUTIC RATIOS, OPTIMAL DOSAGE FACTORS, AND A THEORETICAL PROGNOSIS IN CLINICAL RADIATION THERAPY

by

LIONEL COHEN, M.B., B.Ch., D.M.R.T.
Radiation Therapy Department, Johannesburg Hospital.

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FIRST PHASE - RADIOSENSITIVITY OF HUMAN TISSUES.

CHAPTER I. INTRODUCTION.

NATURE AND SCOPE OF THE RESEARCH.

Ionizing radiation has developed into what is probably today the main weapon in the fight against cancer. In spite of all other developments in cancer research and clinical management, radiation remains the only means by which malignant tumours in man can be made to regress fairly regularly with restitution of more or less normal structure. The common link between the biological mechanisms underlying radiation and cancer is suggested by the unique role played by the nucleic acids in both situations. The action of radiation in altering nucleic acid structure, that is the primary 'Mutagenic' action has been interpreted as a distortion in 'information' content of the genetic material and its antigenic products (* 161, 43). Similarly, the induction of cancer apparently entails a somatic mutation leading to a failure in 'information' transfer, alteration in antigenic character, and hence loss of an essential link in the feedback control of cell growth (* 31).

No attempt will be made in this thesis to review the complex and varied science of medical radiation biology. A complete survey of the extensive literature in this field is already available (* 55). The purely physical aspects concerning the generation and absorption of ionizing radiations will not be elaborated as they are adequately dealt with in several standard texts. Radiochemistry, a vast field of research in itself (* 151), has been surveyed in several expositions (* 14, 55). Similarly, the important cytological effects of radiation have been fully covered in the classic text on the subject by Lea (* 115), and the histopathological changes described in detail in other recent publications (* 22).

This thesis is limited to a systematic and it may be hoped, a useful, review of all those aspects of radiation biology concerned with the reactions of human tissues and tumours to ionizing radiation. The large number of physical, chemical and biological factors affecting their radiosensitivity are assessed, subjecting the available data to statistical analysis as far as is feasible. Methods are developed for modifying such reactions and manipulating the appropriate parameters so as to suit the strategy required by each particular patient in order to eradicate his tumour.

The research to be reported in this thesis has evolved through three phases of development. In the first the writer reviews all pertinent quantitative information on the radiosensitivity of human tissues available in the radiological literature, subjecting published data to statistical analysis so as to define this parameter as rigorously as possible. The median effective doses, and the coefficients of variation, for specific types of reaction under specified standard conditions of treatment are estimated, and the limits of precision are defined.

The second phase of this investigation consists of an empirical analysis of the many technical factors affecting the radiosensitivity, and introduces some parameters measuring the magnitude of these effects, using biometrical methods developed over the past 10 years both in this Department and abroad.

The influence of quality (photon energy), time (protraction and fractionation) and volume (field size and shape) factors upon the separate radiosensitivities of human skin and certain specified tumours is determined. The effect of each of the three variates upon the intensity of the skin reaction is examined independently, by subjecting published data to the appropriate statistical manipulation, and conjointly, by a least-squares regression analysis of the reaction in 150 patients treated in the Department. A similar analysis is then

carried out for human cancer. The effect of the variates on curability is estmated through a modified log-probit assay on 100 epidermoid and 60 mammary carcinoma cases. Empirical parameters appropriate to the variables tested are determined, and a composite 'iso-effect' formula applicable to the complex situation is derived.

In the third part of this work the interaction between the sensitivities and tolerances of normal tissues and tumours is studied. The methods described therein are developed by the writer exclusively from data derived in the Radiation Therapy Department of the Johannesburg Hospital. They include several previously published reports, suitably amended in the light of more recent findings, as well as some unpublished newer observations.

Applying the iso-effect formula to both skin and tumour the therapeutic ratio (ratio of tumour lethal to tissue tolerance doses) is computed with due regard to the various possible combinations of technical factors. It is shown that the prognosis, in a strict statistical sense, is a function of this ratio, and that, in most cases, a single optimal dose, giving the greatest theoretical probability of uncomplicated cure, can be computed from these figures. Some practical 'optimal dosage' nomograms are derived, and it is concluded that the method could be developed so as to devise individualised and well-balanced prescriptions for clinical cancer therapy.

The logical structure of this analysis precludes the format and presentation commonly followed in an academic dissertation. There will be no attempt at a formal subdivision of this work into the conventional separate headings. Instead it will follow the mathematical sequence imposed by the nature of the argument. In so doing, it has been found necessary to pool all available knowledge on many specific experimental and clinical measurements, often combining data compiled from the literature with the writer's own experimental material.

In most instances this was the only possible way to obtain sufficiently well-determined estimates of the particular parameters required in order to take the next step in the calculation.

PHYSICAL CONSIDERATIONS.

Ionizing radiation consists of two main groups of physical entities-electromagnetic quanta or photons, and energetic particles or corpuscular radiations. All biological affects of radiation are necessarily preceded by physical processes taking place in the absorbing medium by which energy is transferred from the beam of radiation to the molecules of that medium. Radiation transmitted through the medium, or scattered outside the irradiated object, produces no biological or chemical effects and is therefore of no consequence in radiation biology.

The corpuscular radiations include the fundamental particles of matter as well as ion-beams formed by accelerating the positively charged nuclei of atoms stripped of the orbital electrons. Of the fundamental particles, the neutrino, though a ubiquitous by-product of almost all nuclear reactions, has such a small probability of capture in any absorbing medium that it produces virtually no ionisation and is, therefore, of no account from the radiobiological viewpoint. Mesons and hyperons, being scarce and transient entities secondary to the absorption of 'cosmic rays' and similar high-energy particles, contribute relatively little energy to the absorbing medium, and so are at present of little practical importance. The role of cosmic radiation, to be anticipated in the extra-terrestrial environment, is likely to be of considerable radiobiological importance, but is beyond the scope of this thesis. On the other hand, the electrons (negative and positive), the nucleons (both protons and neutrons), and the rather more heavily charged positive ions, are all powerful ionizing agents of considerable practical importance in biology and medicine.

The electromagnetic spectrum consists of a wide range of more-or-less energetic photons, characterised by a periodic wavelike field propagated in vacuo at a constant velocity (c) of 3×10^{10} cm/sec. They carry no electric charge, and have zero mass apart from the relativistically associated energy-mass equivalence. The frequency (ν) and wave-length (λ) of a photon are functions of its energy (E), hence $E = h\nu = hc/\lambda$, 'h' being Planck's constant.

ENERGY AND DOSIMETRY.

It is convenient in describing those radiations to introduce an energy unit smaller than the erg and more directly associated with easily measurable factors such as the generating voltage. The usual unit, the electron-volt (eV), is defined as the quantity of energy acquired by an electron, or any particle carrying a unit electronic charge, accelerated through a potential difference of one volt. It is numerically equal to 1.6×10^{-12} ergs.

It should be noted that only those radiations carrying quantum energies in excess of that required to break chemical bonds in organic molecules, that is, the order of 2 to 3 eV, can have any significant biological action. Since 33 eV are required for actual ionisation (*20), it is only that portion of the electromagnetic spectrum ranging from the ultra-violet bands and shorter wave-lengths that can rightly be classified as 'ionising radiations'.

The chemical and biological effects of radiation are quantitatively related to the amount of energy absorbed in the irradiated medium (* 94). The unit of absorbed dose of ionizing radiation, the 'rad', is defined in terms of the quantity of energy absorbed per unit mass of material, and is equal to 100 erg/gm. In practice, this quantity can seldom be measured directly, and the absorbed dose has to be calculated from another, more readily measured, parameter, namely the amount of ionization produced by the radiation in air at the

point of interest. Practical radiation dosimetry is based upon the quantity of energy absorbed in the ionisation process. For this purpose, the 'rontgen' or 'r-unit' has been defined in terms of the quantity of radiation such that the associated corpuscular emission in 1 cm^3 of air at normal temperature and pressure produces ions carrying a total of 1 electrostatic unit of charge (see list of definitions) (* 94).

Thus while the rontgen is appropriate for measurement of ionizing radiation dosage in air, the rad is the unit applicable to radiation absorbed in denser media, such as tissue, or solutions of radiochemical interest. With particulate radiations and photons of very high energy, measurement of the rontgen cannot be realised in practice, but the rad remains a practicable and accurate measure of absorbed dose under all conditions.

The energy used in producing 1 ion-pair in air (W) averages 32.5 eV or 5.2×10^{-11} ergs (* 20). Given that the electronic charge (e), that is the charge on one ion, is 4.18×10^{-10} e.s.u., the energy absorbed in one gram of air per rontgen can be calculated, and is shown to be $E_{air} = \frac{W}{.001293 . e} = 84 \text{ ergs/gm.r.}$ In air, this figure is constant, and practically independent of the quality of the radiation. In water, and for practical purposes also in tissue, E = 84 ergs/gm.r for low-voltage radiation, and ranges with increasing energy, up to 93 ergs/gm.r. for hard gamma rays. Since the rad is always equal to 100 ergs/gm, it is a slightly larger unit than the rontgen, but the ratio of rads per rontgen in water or soft tissue ranges from 0.90 to 0.97 with increasingly hard radiations.

In most radiobiological experimental arrangements, as in clinical radiotherapy, the incident beam will be calibrated in 'r/min' in air for a given set of technical factors. The corresponding dose-rate in 'rad/min' at the surface of the tissue or equivalent material, and at various depths below that surface, is then obtained from standard 'back-scatter' and 'depth dose' tables (* 91).

TRANSITION EFFECTS.

In computing absorbed dose from a beam of known intensity in air, it is often necessary to make some allowance for transition effects as the beam passes from one medium to another of differing density or atomic number. At the interface between air and tissue at the entrance portal of a rontgen beam, or between implanted radioactive sources and the adjacent tissue, the absorbed dose is not proportional to the photon flux, since the predominantly forward scatter of the secondary electrons results in a rising gradient of ionization for some short distance beyond the interface. This distance, before full electronic equilibrium is established, ranges from a fraction of a millimeter with soft radiations to several centimeters with very high energy radiations. There is also a falling gradient at the exit portal where the beam re-enters the air phase, due to loss of the back-scatter component.

In materials containing elements with atomic numbers substantially higher than that of water or soft tissue, the ratio of rads/rontgen will be considerably greater than the value of 0.90 obtaining in tissue equivalent absorbers. The photoelectric absorption coefficient depends on the quality (wave-length λ) of the radiation as well as the atomic number (Z) of the absorbing medium, and is generally proportional to the expression $Z^4 \lambda^3$. Thus a very marked increase in the photoelectron intensity will appear in the vicinity of heavier elements irradiated with sufficiently 'soft' radiation. When mammalian bone, for example, is exposed to rontgen radiation of conventional clinical quality (200 kV), the tissue in its immediate vicinity absorbs about 2 rads per nominal rontgen delivered, and this factor can become as large as 5 rads per rontgen at low kilovoltages (* 168). Similarly, dosimetric errors ranging between 24% (HVL 3 mm Cu) and 68% (HVL 3 mm Al), have been reported in the case of tissue-cultures irradiated on glass (* 129).

All the foregoing physical processes have to be taken into account before any radiobiological experiment or radiotherapeutic result can be analysed with any degree of precision. In this regard it should,

however, be borne in mind that until very recently all clinical and biological desimetry was expressed in terms of tissue rontgens. There have also been large discrepancies in dosage standards in different centres. Errors in estimate of the so-called international rontgen have differed by as much as 15%, and the factor relating rads to 'rontgens' appeared more in the nature of an 'exchange rate' than a consistent physical datum (* 57). Since this 'rate' ranged from 0.9 to 1.0 rads/rontgen at conventional qualities, some of the data used in this survey, (particularly in the case of Tables III, IV, and V), while not strictly convertable into rads, may equally well be considered 'rads' (taking the upper limit of the range) as 'rontgens' (which would assume its lower limit).

In the case of measurements made in this Department, careful comparisons of our substandard dosemeters with those of the National Physical Laboratories at Pretoria and in the United Kingdom, as well as with chambers recently calibrated by the National Bureau of Standards in the United States, over the past 10 years, have shown the Johannesburg 'old rontgen', upon which Tables VII, VIII and IX are based, to be a 'strong' one, and numerically equivalent, at least in the conventional quality range, to almost exactly 1.00 rads. This propitious circumstance permits us to interpret readings in these tables in terms of rads without significant loss of accuracy.

All quantitative data in the following chapters are presented on the assumption that the necessary elementary physical precautions and corrections have been applied, and unless otherwise stated, all doses are given in terms of true absorbed dosage at the point of interest, expressed in rads.

SUMMARY OF CHAPTER I

The physical mechanisms underlying the absorption of ionizing radiation in tissues are reviewed. In particular, the principles of radiation dosimetry, insofar as they affect reactions in the tissues and tumours of the various subjects to be studied, are considered in detail.

CHAPTER II. STATISTICAL CONSIDERATIONS IN ASSESSING THE RADIOSENSITIVITY OF HUMAN TISSUES AND TUMOURS.

In many forms of human cancer the application of ionising radiations will, under certain critically controlled conditions to be described, result in complete and permanent regression of the growth with restitution of normal structure and function in a fair proportion of cases. This pertinent fact is one of the most important aspects of the science of radiation biology. It is becoming clear that the art of clinical radiation therapy depends to a great extent upon the development of methods to ensure that irradiation will always result in such consistent and well-defined effects on the tissues.

In order that a desired effect should be obtained with reasonable certainty, a precise measure of the quantity of radiation delivered to, as well as the radiosensitivity of, the tissue concerned, are both essential. Modern methods of radiation dosimetry have furnished adequate means for delivery of precisely determined quantities, or physical doses, of ionising radiations. On the other hand, radiosensitivity is a measure of a biological dose-response relationship, a statistical concept with considerable inherent variability. It can, other things being equal, be estimated in terms of the physical dose required to produce a standard reaction in all or a specified proportion of individuals tested.

An estimate of radiosensitivity could be one or other of two main types, based respectively on quantal and graded responses (* 145). Quantal methods entail counting the proportion of individuals undergoing an all-or-none response at various dosage levels. Commonly used examples include the estimation of the 'median lethal dose' for total body irradiation, the 'threshold erythema dose' for human skin, the 'median effective dose' for inhibition of tumour growth, and so on.

Grade responses generally entail measurements of quantitative changes in the tissues which can be correlated with the radiation dosage delivered, such as observation of survival time after total body irradiation, changing blood counts, photometric estimation of intensity of the skin erythema, rate of change of tumour volume, the degree of greying of animal hair, on the diminution of tail length of adult mice whose tails were irradiated in infancy.

In clinical radiotherapy the 'median lethal dose' (LD - 50) would be the appropriate quantal parameter for describing the radiosensitivity of a tumour and the 'median effective dose' (ED - 50), for any suitable end-point reaction, in the case of other tissues. As in all biological sensitivity assays, two additional parameters, measuring the variation among individual animals or patients on the one hand, and random dosimetric errors on the other, that is, the 'coefficient of variation' and the 'standard error of the median' respectively have to be taken into account. The quantal reactions in radiation biology, as well as in clinical radiotherapy, are amenable to analysis by the 'probit' method (* 61), by which means the three parameters can be derived. Given these parameters one can, by appropriate statistical methods, compute the dose required to produce the desired effect in all or in any given proportion of cases.

A number of local and systemic radiation reactions are amenable to this type of analysis. Among these, the best example of reactions to local irradiation is given by the skin erythema and its associated changes, though almost all other tissues show analogous effects. With doses below a well-defined threshold value, say less than 300 rad, there are no visible changes. After a sufficient single dose of radiation (say 1000 to 2000 rad), there is firstly a transient reddening visible a few hours later and usually fading within a few days termed the early reaction ('Fruherythem'), which is not a true radiation effect but is

possibly a response to fluorescent U-V energy. This is followed by a latent interval of 2-3 weeks during which intracellular changes, and abnormal intercellular exchanges, are taking place but without any macroscopic or visible alteration. Next comes the main reaction ('Haupterythem') starting with the erythema, characterized by a sharp reddening of the irradiated area; then the second degree, or dry desquamative reaction with superficial peeling; and the third degree, or moist exudative reaction, a painful blistering of the treated skin considered to indicate the skin tolerance limit in clinical radiotherapy. Larger doses may produce necrosis in which most of the irradiated tissue dies and is sloughed away leaving a permanently non-healing ulcer.

There are associated changes in the adnexal structures. Epilation starting in the third week may be permanent or hair may regrow depending on dosage; sebaceous and sweat glands may be destroyed; pigment may increase or decrease giving a mottled appearance, and vascular walls are so altered as to give the characteristic telangiectasis. In most animals (but not in man) hair pigment is lost and on regrowth a degree of greying is usual. Many other tissues will undergo similar inflammatory reactions after irradiation. Radiation mucositis, pneumonitis, nephritis and myelitis are commonly observed complications of irradiation therapy.

Particularly sensitive to local irradiation are rapidly proliferating tissues such as those of the gonads, the bone marrow, the growing epiphysis, lymph nodes, thymus and the intestinal mucosa. In these organs there is a constant turnover of cells, and their integrity can be maintained only through continuous cell division. Doses of a few hundred rad are sufficient to destroy the proliferating parenchymal elements, which are then replaced by surviving connective tissue cells, leading to a fibrosis of the irradiated organ. For

example, permanent destruction of the ovary, virtually an irradiation castration, can be produced with under 1000 rad and the testis will atrophy with even smaller dosage. Actively secreting organs, the salivary glands for example, are also radiosensitive in the sense that all secretions will cease after similarly small doses.

QUANTITATIVE ASPECTS OF HUMAN RADIATION REACTIONS.

Analysis of the human skin erythema reaction has yielded a large body of useful quantitative data. One suitable end-point studied, is the threshold erythema dose (TED), defined by Quimby as that quantity of radiation giving a faint reddening or pigmentation of the skin, visible in two to four weeks in 80% of exposed cases (* 127). While a certain degree of subjectivity enters into this type of assessment, the reaction is remarkably consistent even among people differing widely in complexion and other characteristics. For the purpose of the statistical analysis required in this investigation, however, a better end-point would be the median effective dose for the first degree erythema (ED - 50, 1°E), which will be defined in a later section. In practice this value will differ little, if at all, from the TED. Under standard test conditions, using say 200 kV radiation delivered at a single short sitting through a 10 cm. diameter circular or square field, the 1°E, ED - 50 for human skin is 700 rad, 95% of individuals reacting between 570 and 860 rad (700 ± 23%)

Further clinical observations (* 104) indicate that doses of 2, 3, or 4 times this quantity correspond to median desquamative, exudative, and necrotizing doses respectively (see table I). The coefficient of variation lies between 10 and 14% in each instance, the distribution being essentially log-normal and best described on a log-probit system (* 44). The general features of these dose-response curves are shown in Fig. 1.

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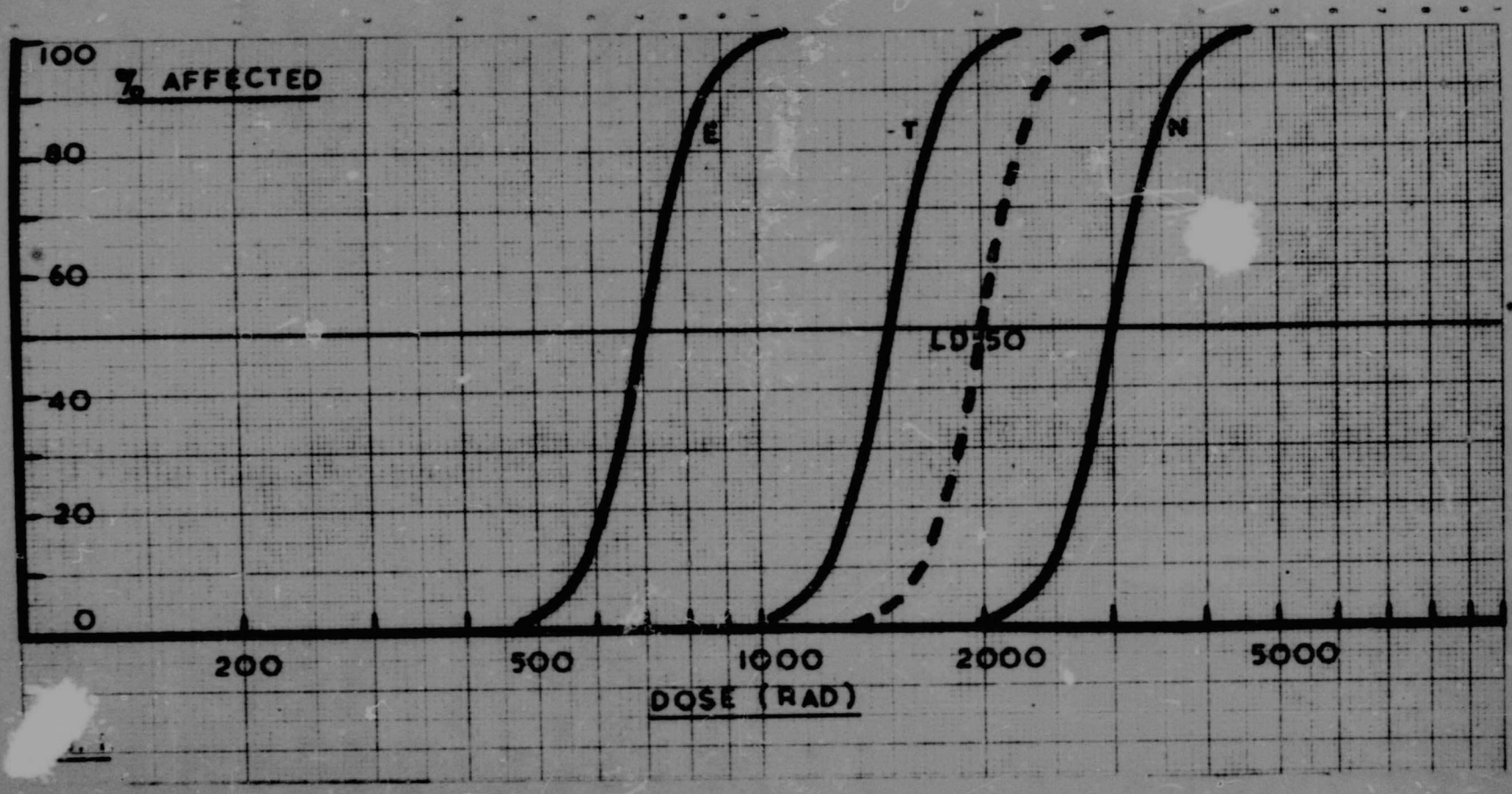

Fig. 1. Sigmoid dose-response curves for radiation reactions in human skin showing the erythema (E), tolerance (T), and necrosis (N) levels for a single exposure at 250 kV on a 10 cm field. The dotted line indicates the cure-rates for epidermoid cancer under the conditions specified.

be defined pragmatically, disregarding individual variation, as the quantity of radiation producing a brisk third degree reaction which will subsequently heal without further damage, being barely smaller than that required to induce necrosis. However, no such uniquely determined quantity can, in fact, exist, because of differences in individual sensitivity. In practice, the 'tolerance dose' can be defined only in terms of a particular dosage level at which the probability of necrosis is tolerably small. Although it might seem at first that the smaller this risk the better, clinical experience shows, for reasons which will be analysed in a later chapter, that it is undesirable to set this limit too low, and a tolerance dose carrying an associated risk of necrosis of no more than 2% is generally considered acceptable.

The third quantitative factor of clinical importance is, of course, the tumour lethal dose, that is the minimum quantity of radiation required to effect a cure in all, or in a large proportion, of treated cases. This quantity depends on the origin and pathological type of the tumour treated. In practice, however, though human cancers vary widely in radiosensitivity, they are generally found to fall into one of three main categories. These include the highly sensitive tumours such as the lymphomata and embryonic cancers which respond to relatively small doses; the radioresistant connective tissue sarcomas, adenocarcinomas of the gastro-intestinal tract, melanomas and glioblastomas in which the lethal dose is in most cases so large as to exceed the limits of normal tissue tolerance; and the important intermediate group of tumours having a moderate sensitivity, but which can often be cured by a judicious choice of technical factors.

It is in this latter group of potentially curable tumours, particularly the squamous cell or epidermoid carcinoma arising in

relatively accessible sites, that the application of radiobiological principles can lead to substantial improvements in clinical cureratos. Their radiosensitivity can be assessed in terms of the statistical median lethal dose (LD - 50), that is the dose which, under specified conditions will cure 50% of treated cases. In practical therapy allowance will be made for individual variation in radiosensitivity, and the (LD - 50) will be exceeded by a factor sufficient to permit a large proportion of permanent regressions. For many technical reasons, which will be analysed subsequently, it is impossible to achieve a 100% cure-rate, and the tumour lethal dose may be accepted as that which will eradicate somewhat over 90% (say LD - 95) of tumours treated.

It is a fact that the radiosensitivity of a given tissue species, and of all tumours arising from any one tissue, is remarkably constant. That is to say that, while the radiosensitivity of different tissues in the body and of similar tissues in different species vary widely, there is a relatively small variation in the radiosensitivity of similar tissues among different individuals of the same species. A study of individual variations of human skin in its reaction to rontgen irradiation by Holmke (* 85) revealed an extremely narrow range of radiosensitivities. While the average erythema dose in this series was 300 r, no subject responded to less than 225 r and at doses over 400 r, all subjects showed a definite reaction. Examination of the data shows it to have an almost perfectly log-normal distribution with a mean of 309 and a standard deviation of 35, or, in other words a coefficient of variation of 35/309 or 12%. Todd's (* 181) data for skin reactions with a different set of technical factors, showed a very similar variability. It can in fact be shown that this coefficient is quite consistent in other human and experimental animal tissues.

For example, all human breast cancers cluster about an average radiosensitivity, or median lethal dose, of about 1270 rad (single

X-ray exposure) with a coefficient of variation of only 11% (* 40). In 95% of patients the minimum lethal dose will lie within 23% (twice the coefficient of variation) of the median value. In human skin cancer the median dose is much larger, about 2000 rad and the coefficient of variation is still only 14% (* 44). Even in the mouse mammary tumour, though the median lethal dose is of a very different order, in fact 5700 rad, the coefficient of variation is around 9% so that individual radiosensitivities also range between ± 20% of the median (* 38). This consistently small coefficient of variation means that with any tumour, a virtual certainty of local cure, at least in well over 90% of treated cases, can be obtained if we ensure that the minimum tumour dose exceeds the median lethal dose by about 20 to 30%. The reaction of host tissues, that is, skin erythema and tolerance doses, as well as systemic and lethal effects, will, of course, also occur within a similarly narrow dosage range.

In any 'normal' distribution, over 95% of individuals fall between two standards deviations of the mean, or, as in the present instance, within twice the coefficient of variation around the median. It then follows that if the median doses shown in Table I are multiplied or divided by a factor of 1.3, one gets the doses corresponding to a 98% and a 2% response respectively. Thus, if under standard conditions, 2800 rad is a 'median necrotising dose', then 2800 ÷ 1.3 = 2150 rad is the dose carrying a 2% risk of necrosis. This happens to be about the same as the 'median exudative dose' which is almost exactly three times the TDD and would produce a third degree reaction in half, and some necrosis in just under 2%, of all subjects exposed. As shown in a later chapter, this level of reaction can, with advantage, be used as a practical estimate of the skin tolerance limit.

Within narrow limits, the larger the tumour dose, the greater is the probability of cure. Similarly, the larger the dose, the more severe

Author Cohen L
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