THE TREATMENT OF MALIGNANT DISEASE BY RADIUM AND X-RAYS

Being A PRACTICE OF RADIOTHERAPY

BY

RALSTON PATERSON

C.B.E., M.C., M.D., F.R.C.S., D.M.R.E., F.F.R.

CHRISTIE HOSPITAL AND HOLT RADIUM INSTITUTE, MANCHESTER

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INTRODUCTION

THE scope of this book is most aptly described by its sub-title—A "practice" of radiotherapy. It is essentially a statement of the principles and practice of the Christie Cancer Hospital and Holt Radium Institute, Manchester. An attempt is made to present clearly, and with a reasonable amount of detail the manner in which radiation is there applied to the treatment of malignant disease. It is necessary to emphasize, however, that there is no intention of implying that the methods and ideas presented are necessarily the best, the correct, or the only methods. It is fully realized that with a specialty developing as rapidly as modern radiotherapy there are many alternative, equally well-founded approaches to the various problems.

It seemed to me that the presentation of one definite outlook would be at the present moment of more value than an attempt to correlate different principles and practices so varied that an attempt at fusion would restrict description to vague generalities. This book must therefore be regarded neither as a complete text-book nor as an attempt to sum up the present state of radiotherapy in general, but rather as one particular practice of that specialty in which it is hoped that a reasonable synthesis of most that is well-tried has been achieved.

Radiotherapy is an evolving specialty, and therefore the practice of any particular time is liable to go out of date with surprising rapidity. All that we can do is to attempt to crystallize the situation at the moment of writing. In the interests of clarity this tends towards dogmatic statement as if the situation were static. It should be kept in mind therefore all the time that practice is far from static, and that steady change is being made all along the line, from the position as described—change which we trust is improvement. The dogmatic presentation should be taken as definiteness of statement, not fixity of opinion.

A practice of any subject cannot be developed without basic principles. It is therefore necessary before developing the detail of technique for any therapist first to make up his mind as far as he can on what foundations he will build. Unfortunately in radiotherapy to-day many of the major issues are still far from finally determined. Examples of these are the nature of the lethal effect of radiation on the normal and malignant cell, the factors determining radio-sensitivity, the real influence of time and intensity factors and the biological significance of wave-length. The fact that such issues are still controversial does not lessen the necessity for having working hypotheses. In keeping with the pattern of this single practice, the first three chapters state the particular principles on which the Manchester methods are based. These principles represent our present interpretation of the existing evidence on the nature of radiation action. Research and further experience will show to what extent the various estimates have been fortunate. Inevitably some of them will ultimately be found wanting, and practices founded thereon will have to be duly amended. Nevertheless, it is better to state one interpretation clearly than to attempt to outline at length the various parts of the evidence, but without a judgment. It is realized, too, that a few of the opinions may very well be called unorthodox, yet they are presented equally definitely and without apology, in that they represent the author's present working hypotheses and are the foundation of what follows.

In radiotherapy to-day, it is impossible to make any justifiable distinction between X-ray therapy and radium therapy. The two are essentially the same in principle and in effect, differing only in those factors which result from the different origin of the two radiations, and which therefore govern their applicability. No practice of radiotherapy can be complete or well balanced unless both are equally available—and in the same hands—and therefore the two are dealt with as one specialty—radiotherapy. On the other hand, it is realized that with conditions as they exist to-day, the actual availability of each may vary. Moreover, there are fields in which either agent is applicable—often with equal prospects, or more often where the difference of value is so slight as to be relatively unimportant. Some attempt, therefore, has been made to keep radium and X-ray techniques distinct in the discussion on each disease, and to outline methods for each where alternatives exist, as, for instance, in the treatment of skin cancer.

One of the outstanding needs of radiotherapy to-day is an organization that provides an adequate and integrated team, including both medical and skilled lay personnel. To achieve this, the whole trend of modern planning is towards centralization of radiotherapy—and possibly of cancer surgery as well—on a comparatively extensive scale. All experience shows that there is a great need for centralization to a single organization of the cases coming from a population unit of at least one million, with the probability of increasing efficiency up to two or even three millions. The comprehensiveness of the integrated team of workers and the scale of equipment which is thus made possible yields immeasurably greater efficiency than can be achieved with small-scale work. Because many such centres are at the present time being created both in England and abroad, a fairly full description is given of the necessary organization, in particular of the way in which the unit should reach out into the territory served so as to contact the patients near their homes, even though providing treatment at what may be a considerable distance.

Certain customary inclusions in such books as this have been omitted. In the first place, statistics of results are not given here, but relevant information on that subject may be obtained from the *Third Five-Year Report of the Holt Radium Institute*, 1940–44 (published by E. S. Livingstone, Edinburgh). Secondly, a knowledge of the physics of radiation is taken for granted. The only physical aspects dealt with are those directly concerned with the practical applications, particularly in regard to the assessment of dosage. Put succinctly, this book starts with, as its medium, gamma-rays after they have left the needles or tubes, and X-rays as a beam of radiation on the patient's side of the filter. Thirdly, the subject has been limited to the *treatment* of malignant disease by radiotherapy, and is only concerned with its clinical features, diagnosis, or even surgical treatment in so far as these relate directly to the problems of radiotherapy. Clinical discussion, therefore, has eschewed matter to be found in surgical text-books or which is common surgical knowledge. The pathological nomenclature used is that which is more or less ordinarily accepted.

In conclusion, it is assumed that after adequate consultation to determine the appropriate treatment, the radiotherapist treating a case is in charge of, and responsible for that case, both in his department, and in the ward. Division of responsibility is not in the patient's best interests.

ACKNOWLEDGMENTS

As has been emphasized, this book is largely a description of the work of the Holt Radium Institute in Manchester. There are, therefore, few members of that organization, whether present or past, whether medical or lay, who have not contributed either directly or indirectly. The list of individuals concerned is too great to mention by name but includes physical, technical, and clerical as well as medical and nursing staff of all departments of the hospital. Indeed, the numbers involved are but symbolic of the integrated team work which is essential in the radiotherapy of cancer.

As will be seen in the various chapter headings, several of my colleagues both in Manchester and in London have collaborated in relation to particular fields in which they have unrivalled knowledge. Such acknowledgment of direct contributions, however, fails to record the fact that some of them have been equally helpful in regard to other parts of the book. This is particularly true of Dr. Margaret Tod. Lastly, although only appropriately recorded for the chapter on research, Dr. Edith Paterson has played a vast part both in the writing and illustrating of the book. In many ways, it would have been more accurate to have put as the author not my name alone but to have coupled this with the names of Margaret Tod and Edith Paterson.

Ralston Paterson.

Christie Hospital and
Holt Radium Institute,
Manchester,
1947.

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CHAPTER 1

GENERAL PRINCIPLES

WHILE we know that irradiation in sufficient dosage is followed by the death of cells, we do not yet know how this death is brought about. Again, we know that different cell types vary in their sensitivity to radiation, but we do not know why this should be so. A vast amount of good experimental work has been done towards elucidating these two points and many theories have been formulated. At the present moment no one of the theories has been adequately substantiated and the discovered facts, with few exceptions, still lack that integration with each other which is necessary for a comprehensive interpretation in the clinical field. They are, nevertheless, the bricks for building the radiotherapy of the future.

Meantime we have to focus our attention on the fact that irradiation at appropriate dosage levels causes cell death, and that these dosage levels are different for the different tumour types and normal tissues that have to be considered.

As a result of clinical experience, there exists a very considerable body of knowledge about the response to radiation of tumours *in vivo*. This chapter is concerned with those principles which have been founded mainly on clinical observation, and on which modern radiotherapy has been built up.

Tumour Lethal Dose.

The value of radiation—indeed the whole basis of radiotherapy—rests on its capacity to destroy certain types of malignant growth *in situ* without at the same time producing destruction of the normal tissues in which the tumour is growing, and which necessarily receive an equal dose of radiation. Growths so destroyed must be relatively sensitive to radiation. Radiation is thus a selectively destructive agent, and is not a refined form of cautery. This selectivity makes possible the conception of a tumour lethal dose.

A tumour lethal dose for any one tumour is that dose of radiation which produces complete and permanent regression of the tumour *in vivo* in the zone irradiated. This is probably not a dose which is directly lethal to each cell of the tumour, either *in vivo*, or, if cultured, *in vitro*, but it is the dose which is lethal to the tumour as a whole, regardless of the mechanism of that lethal action.

I believe, for reasons to be discussed later, that tumour lethal dose, although it varies widely for tumours of different histological species, shows only a narrow range of variation for tumours of the same species. Irradiation of a number of tumours of any one species with varying doses leads to the belief that below a certain dose level no tumour, or practically no tumour, will be destroyed; but as thereafter the dose is raised, destruction of tumour will occur in an increasing percentage of cases, until a level is reached at which the dose is consistently lethal in the species under consideration. It must be remembered that tissue tolerance frequently prevents the giving of such maximal doses, but this practical difficulty does not alter the fact that such an effect is possible. Put into graphic form this relationship between dose and lethal effect can probably be expressed as shown in Fig. 1. 1.

This expression of the relationship between lethal effect and dose was first propounded by Holthusen, and seems a reasonable interpretation of the present known facts, and in keeping with many experimental findings. Accepting this as a working hypothesis, various consequences follow; there is a dose—Point A, (Fig. 1. 1)—below which no tumours respond; at the upper curve of the sigmoid there is a point—TLD—at which the majority of tumours, say 80 to 90 per cent., resolve completely; above that point the dose has to be increased very considerably to gain any appreciable rise in the percentage of tumours showing lethal effect. In practice, therefore, this TLD level may be accepted as a useful single figure expression of tumour lethal dose for a "species," and might be defined in words as "That dose which, *in vivo*, produces lethal effects in the treated area in a large percentage of irradiated growths of the species under consideration." In all that follows, this conception will be accepted, and this definition of tumour lethal dose adopted. From this argument, it is seen that treatment at dosage levels somewhat below the

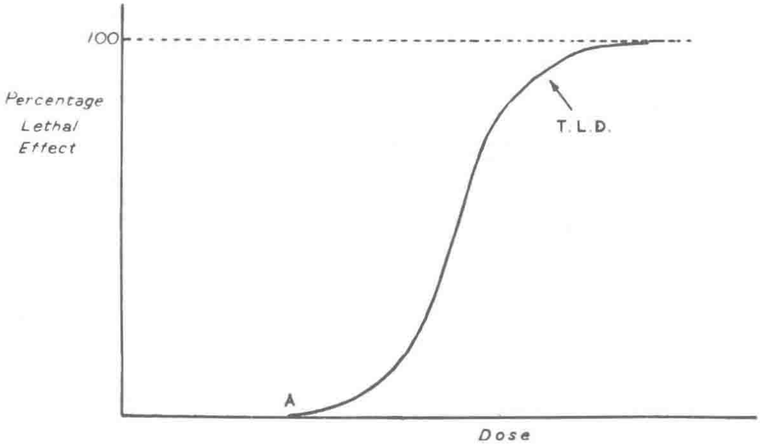

FIG. 1. 1.—THE PROBABLE EXPRESSION OF THE RELATIONSHIP BETWEEN DOSE AND LETHAL EFFECT FOR ONE SPECIES OF TUMOUR.

tumour lethal dose (TLD) will produce resolution, but in fewer cases, while a still lower dose will never produce a lethal effect: at the other end of the graph a small fraction of cases will respond only to doses so high that the risk is not justified as a routine merely to be sure of reaching this small fraction. This last phenomenon is graphically illustrated in tissue culture experiments, where it is found that occasional cultures survive a dose three and even four times the amount ordinarily lethal to such cultures.

It will probably be of value to consider an example taking the "species" squamous cell carcinoma as an illustration. My experience of the response of this particular tumour to gamma radiation for the overall time period of eight days can be expressed by the curve shown in Fig. 3. 2. The dose points on the X abscissa represent the *minimum* dose in the irradiated area. Following the convention outlined, the dose 5,500r can be taken as a single statement of lethal dose for squamous-celled carcinoma, under the given conditions of eight days continuous radium treatment.

If these premises are accepted, an attempt must ultimately be made to arrive at a similar statement of tumour lethal dose for each species of tumour. Unfortunately sufficient data regarding the sensitivity of most neoplasms is lacking.

Tissue Tolerance.

Having arrived at one conception of the quantitative relationship between dose and effect on a single irradiated tissue—tumour—it is reasonable to suppose that the same kind of relationship exists for other irradiated tissues, e.g. muscle, blood vessels, nerve cells, etc.

For instance, in regard to the dose required to produce permanent destruction of skin (i.e. necrosis), the relationship can probably be expressed as in Fig. 1. 2.

On this basis, there is a point, in the region of the point *Nec* on the graph, when the percentage of necrosis begins to rise fairly rapidly with increasing dose, but below which dose has to be reduced greatly to eliminate with certainty the possibility of a necrosis occurring in the skin of the exceptionally sensitive variant.

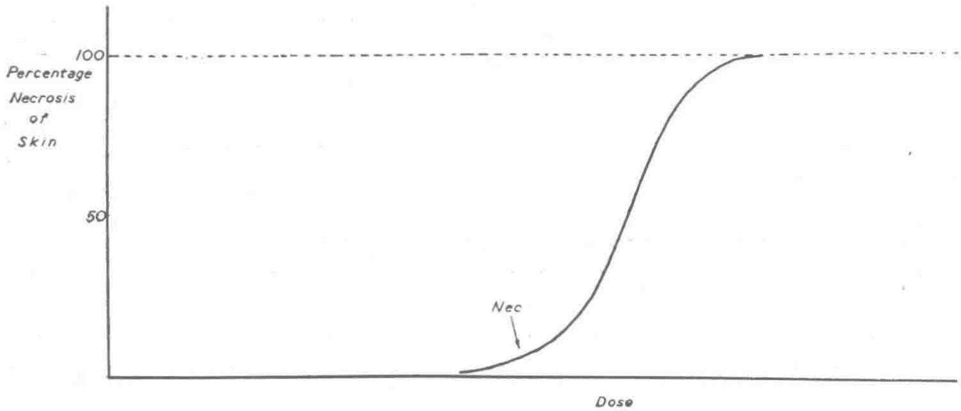

Fig. 1. 2.—Possible relationship between dose and incidence of skin necrosis.

Where therapy is determined by the limited sensitivity of the tumour, a high dose has to be given to obtain the best results and the small fraction of necrosis, say not over two or three per cent., is justifiable.

Therapeutic Ratio.

So far the relationship between dose and lethal effect for one tissue has been discussed as if it were an isolated problem. It cannot be so regarded, and the therapeutic possibilities of using the killing action of radiation depend not on one factor, but on the ratio between two factors, tumour lethal dose and tissue tolerance. To this we might give the name "Therapeutic Ratio." I consider this conception so important that it must be kept constantly in mind when the principles underlying the therapeutic action of radiation are examined. It is this ratio which determines whether any particular lesion can be treated easily, with difficulty, or not at all. One easy method of clarifying and of bringing out the implications of this conception is by illustration.

Methods of increasing tumour sensitivity or of enhancing the lethal action of radiation are often suggested; for instance, it may be claimed that the addition of a specific substance X to the blood stream increases the sensitivity of certain tumours to radiation. This of itself is valueless, unless it can be shown that the sensitivity of normal tissue in which the X is also circulating has *not* likewise been increased to the same degree.

When we attempt to improve technique, we have to be concerned not only with the killing capacity of radiation to tumour, nor solely with increasing the tolerance of tissue, but always with the ratio between these two. If, for example, low dosage rate (low intensity) does provide, as is claimed, some increase in skin tolerance, it does not follow that this is better radiotherapy. Advantage only accrues if it can also be shown that such increased tolerance is associated with no corresponding increase in tumour tolerance. A substance or a method which doubled the resistance of a tumour would still be of great value if at the same time the tolerance of normal tissue were trebled.

Clinically, therefore, the sensitivity or resistance of tumours must be considered only in terms of this conception. The term radiosensitivity is open to misconception and merits definition. As used here it is to be considered entirely synonymous with *local radiocurability* (i.e. in the treated zone) and in no sense refers merely to *rate of regression* following radiation except in so far as the two, naturally, tend to run parallel.

Sensitive tumours are those in which the therapeutic ratio is high, the normal tissues tolerating doses of several times the magnitude of the tumour lethal dose.

Tumours of limited sensitivity are those in which, although the tumours are more sensitive than normal tissue, this ratio is low, and the permissible dose exceeds the TLD by only a small fraction thereof.

Resistant tumours are those in which the dose required to produce lethal action in tumour is almost as great as, or greater than, the destructive dose for normal tissue.

These three groups are not, of course, distinct, but represent arbitrary clinical sub-divisions in a continuous scale of radiation response. This grouping according to radiosensitivity will be discussed in detail later. The distinction made, however, between sensitive tumours and those of limited sensitivity is clinically important, inasmuch as it differentiates two major groups of common tumours which will be referred to frequently in this chapter.

These two factors, tumour lethal dose and therapeutic ratio, are paramount in radiotherapy. They have therefore been stated first, and the simplest method of considering general principles is to arrange them round these two main headings, and examine seriatim the various factors which affect them.

FACTORS AFFECTING TUMOUR LETHAL DOSE

The three most important items needing consideration in relation to tumour lethal dose are:

Dose.
Wave-length.
Time (including interval and dosage rate).

DOSE.

In radiotherapy, dose is the measure of the quantity of radiation absorbed at a given point, e.g. in the centre of the tumour or on the skin surface. Before the development of satisfactory physical methods for measuring radiation quantitatively, dosage units were, for many years, based on various biological effects produced by radiation, the most important of these being the erythema dose. It is now possible to measure dosage in purely physical terms, and this is preferable to even the best biological dosage units. In radiation therapy, the internationally accepted unit of radiation is the roentgen, the definition of which (International Congress of Radiology, Chicago, 1937), is now as follows :

> " The roentgen shall be the quantity of X- or gamma-radiation such that the associated corpuscular emission per 0·001293 grams of air produces, in air, ions carrying 1 e.s.u. of quantity of electricity of either sign."

In this book the roentgen is accepted as the dosage unit to be used for both X-rays and gamma rays. The measurement of radiation in roentgens is a measurement in terms of the ionization produced, and not directly in terms of the energy released by that radiation. Although ionization and energy absorbed run parallel to a large extent, this is by no means invariable. The divergence, which at times causes slight confusion, will be discussed later. It is advisable to consider separately how the roentgen is used for X-rays and for radium.

X-ray Therapy. The definition given above allows us to consider a roentgen of radiation as that which produces a certain quantity of ionization in a small air-filled cavity. The dose delivered at any point is therefore indicated by measuring the ionisation which would be produced in such a very small (theoretically infinitely small) cavity of air at that point. Fig. 1. 3. indicates this air-filled cavity in the three different situations which concern us.

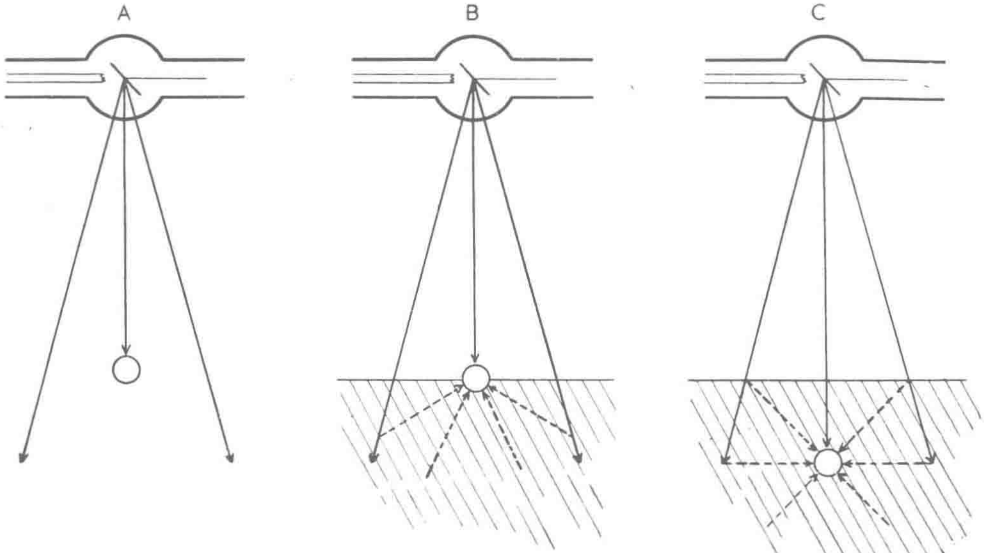

FIG. 1. 3.—THE CONDITIONS UNDER WHICH THE IONIZATION IN A SMALL AIR-CAVITY CAN BE ASSESSED A—" In air," B—On a surface, C—In tissue.

While " in air " measurements may be used in assessing the output of the X-ray tube they cannot be used as a clinical measure of dosage and it is unfortunate that this practice ever developed. The quantity of radiation being absorbed on a surface is often referred to as the " skin dose " or the " given dose." The quantity of radiation being absorbed at a point in the radiated volume of tissue becomes the basis of measurement of the " tumour dose." The only true expressions of *dosage in roentgens* in practical therapy are the surface dose and the tissue dose which must therefore form the basis of all statements or prescriptions of skin dose and tumour dose. It is essential that the " in air " method of computation be discarded as a serious hindrance to accurate thinking on the dosage question.

When dosage is computed in roentgens it is assumed that the actual ionization in water or tissue at any point runs exactly parallel to ionization in air and that the latter becomes therefore a true index of the ionization being produced. This is, for all practical purposes true for water, and for most tissues, and the roentgen used in this way is a very convenient method of assessing dosage, provided that it is remembered that there are notable exceptions, the characteristics of which will be discussed in the later consideration of wave-length effects.

Radium Therapy. The use of the roentgen in gamma-ray therapy has been accepted internationally in theory (Chicago Congress, 1937), but formal international agreement has not yet been reached as to its evaluation. The basis of the roentgen for gamma-rays rests on the measurement in r of the radiation at 1 cm. distance from a point source of radium filtered by 0·5 mm. Pt. In this book that value is taken as 8·4r per hour per milligramme.

The graphs and rules given in this book are based on the above assessment, and by the use of them the dose at any point from appropriate arrangements of radio-active foci can be determined. The use of the graphs in this way involves an assumption, namely, that the dose in tissue from any such arrangement is the same as that obtained from the same arrangement of foci in air or in a vacuum. This is not strictly the case, but owing to the fact that scatter and absorption approximately cancel each other out, it is sufficiently accurate for all practical purposes.

WAVE-LENGTH.

The two therapeutic agents receiving most attention in this book are X-rays in the range 60–250 K.V. and gamma-rays as utilized in all forms of radium therapy. The radiation produced by either is a mixture of wave-lengths—a heterogeneous not a monochromatic beam—and for descriptive purposes it may be necessary to define in some way the quality of the radiation. This is often done by stating its average wave-length, but more commonly by a statement of the half value layer, that is, the thickness of aluminium, copper, tin or lead which cuts the intensity of the radiation under consideration by 50 per cent.

The main difference in physical properties between long and short wave-lengths is the difference in penetrating capacity. The shorter the wave-length the greater the ability to deliver dose at a depth. Apart from X-rays in the 60–140 K.V. range, this difference is, however, not important within the usual treatment range of 200–500 K.V., where even with heavy filtration only minor improvements in depth dose are achieved owing to the compensating effect of scatter. Gamma-rays of radium are much more penetrating but in practice the possibility of achieving good depth dose at a point below a surface is determined more by the focal-skin distance than by pure penetrative capacity. Penetration may prove of great importance with the newer X-ray plants operating at over one million volts.

Another factor of importance which must be considered is the bearing which changes in wave-length may have on clinical response. The weight of clinical experience, as I interpret it, would seem to indicate that within the range of wave-lengths used in present-day clinical practice—that is, X-rays from 60 to 1,000 K.V. and the gamma-rays of radium—response to treatment is unaffected by wave-length, all other factors being equalized. For many years, controversy raged around the subject of specificity of wave-length. One school of workers believed and taught that quite apart from all questions of depth dose and a differential absorption of different wave-lengths in different tissues, the shorter wave-length was superior to the longer as a therapeutic agent in malignant disease. Most present-day workers do not believe in the specific advantage of shorter wave-length and hold that at least in so far as lethal effects on tumour tissue and normal tissue are concerned, and in particular as regards the relationship between them, it is immaterial how radiation energy is applied to an irradiated volume.

This problem is important, chiefly in relation to the choice between X-rays at ordinary kilovoltages of 200 to 250 K.V. and gamma-rays (or homologously X-radiation at 1,000 K.V. and upwards). It also has a bearing on the question of filtration of X-rays.

The statement, however, that from a clinical point of view, wave-length *as such* is unimportant, must not be allowed to mask the fact that there are great differences in physical characters (e.g. depth doses) associated with the different wave-lengths. The general principle nevertheless is of considerable importance in that if we accept it we can, by and large, interchange experience of X-ray and gamma-ray therapy, and look upon these as interchangeable media except in so far as important differences in method of application and treatment period may affect the situation.

It is insufficiently realized that it is almost impossible, except as a specially devised experiment of extremely limited scope, to compare gamma-rays and X-rays under strictly identical conditions of usage. I believe that if such strict comparison could be made possible, it would show that gamma-rays and X-rays were, in fact, clinically interchangeable for equal amounts of energy absorbed in any irradiated tissue. The comparison in question is difficult in clinical practice in that X-rays and gamma-rays differ from each other in two very salient particulars.

(*a*) X-rays in general have to be employed at higher dosage rates applied as short intermittent exposures. The conditions under which radium is used usually necessitate continuous, or at least prolonged radiation at very low dosage-rates.

(*b*) The use of radium permits, in many cases, much smaller volumes to be irradiated than is possible with X-rays. The most obvious contrast is between needle-implant and cross-fire small-field radiation, the difference being the additional tissue irradiated by each X-ray beam in transit to the volume it is designed to treat. Even in the case of superficial lesions, a single X-ray field irradiates more tissue than, for example, a radium applicator in that the resultant depth dose gradient is less steep. Probably the only truly comparable situation in this respect is that between superficial radium applicators and 60 K.V. X-ray therapy, and even there the time-factors are very different.

For these reasons, there are few circumstances in which it is possible to interchange X-ray dosage and gamma-ray dosage, either in relation to tumour effects or to tissue tolerance. For the same reason, it is practically never possible to summate roentgens directly for X-ray and gamma-ray treatments. As a consequence, techniques have to be developed independently for radium, X-ray and for each type of combination of the two, and tolerance levels assessed as separate determinations. Within this limitation, however, knowledge of response to either of the two agents is equally applicable to the other provided only that the technique most appropriate to the agent in use be employed. There is, for instance, no real comparison between a radium implantation of the fauces and whole neck X-radiation using large fields, yet it is found in practice that a fauces implant is, in a great degree, interchangeable with long-term, small-field, cross-fire X-ray treatment, each at the appropriate physical dosage for the over-all times employed.

Another important corollary to this principle of non-specificity of wave-length is the fact that X-rays cannot be safely employed after full dosage radium, nor a radium treatment risked in tissue which was previously irradiated to tolerance levels by X-rays.

This question has been analysed at some length because there is considerable misconception as to the real issues involved and short wave-length irradiation is credited with advantages which are not inherent in the wave-length but are indirect consequences of its manner of production and application. I feel that when all the realities of the situation become clarified, effect in both tumour and normal tissue will be found to be a factor solely of the radiation energy absorbed and to bear no relationship to the wave-length delivering that energy. This generalization in regard to the clinical field does not, however, mean that one can deny that differences do exist where intra-cellular effects are examined as an experimental problem.

It should be noted at once that energy absorbed does not necessarily run parallel in all circumstances to dose in roentgens. Dose in roentgens, in tissue or on a surface, is only an absolute mirror of energy absorbed if the tissue involved absorbs exactly as it would were it made of compressed air of the same density as that tissue. As air and water are sufficiently equivalent to each other in the average atomic number of their constituent substances and as the human body for the most part is water equivalent, dose in roentgens in most tissues is a true index of energy absorbed and would produce identical effects, dose for dose, for radiation of any wave-length. Certain tissues, however, contain substances which include atoms of higher atomic number than the average. The chief of these tissues are skin and bone, the former on account of the sulphur content of keratin, the latter on account of the calcium. In these, as has been shown by Mayneord and by Edith Paterson, the additional characteristic ionization over and above the ionization accounted for by the dose in roentgens is considerably greater with X-rays than gamma-rays and therefore the radiation energy absorbed, dose for dose, is greater. I believe that this, or some such process, is what accounts for the reported increase in tolerance of human skin to short wave-length radiation. This gives such short wave-length radiation a purely physical advantage when radiation is passed through skin to deep tumour, but this advantage is only quantitative and merely augments the advantages due to greater penetration ; it is in no sense biological.

To summarize, I propose in this book to accept as a working hypothesis that there is no specific biological value in shorter wave-length radiation, but that in certain circumstances advantage does arise from purely physical properties such as increased penetrating power of the shorter waves, greater localizability of radium, or lessened characteristic absorption in skin. Clinically, the findings and experience of gamma ray and X-ray therapy can be transferred from one to the other with appropriate adjustment for divergent time factors, and in many circumstances methods can be devised by which either may be used equally well.

TIME FACTORS.

As important as considerations of quantity and quality of radiation is the study of the time over which radiation is spread and of the method of fractionating the total dose. In order to analyse the effects of time and interval clearly, the effects of these two factors must be considered separately.

Overall Time. Consideration must first be given to the effects of variation in the overall duration of exposure—assuming for this analysis that such exposure is continuous *or equivalent thereto.* This then becomes a datum line with which all other arrangements are compared. The outstanding fact is that in clinical therapy effect varies enormously with time. The general rule is that the longer the overall duration of treatment the greater the dose required to produce any particular effect. For this reason a mere statement of dose does not give enough information. It should be an invariable rule to state " dose in relation to time " in any matter relating to clinical therapy. An illustration of the relationship between dose and time for one particular effect—skin tolerance—is shown in Fig. 1. 4.

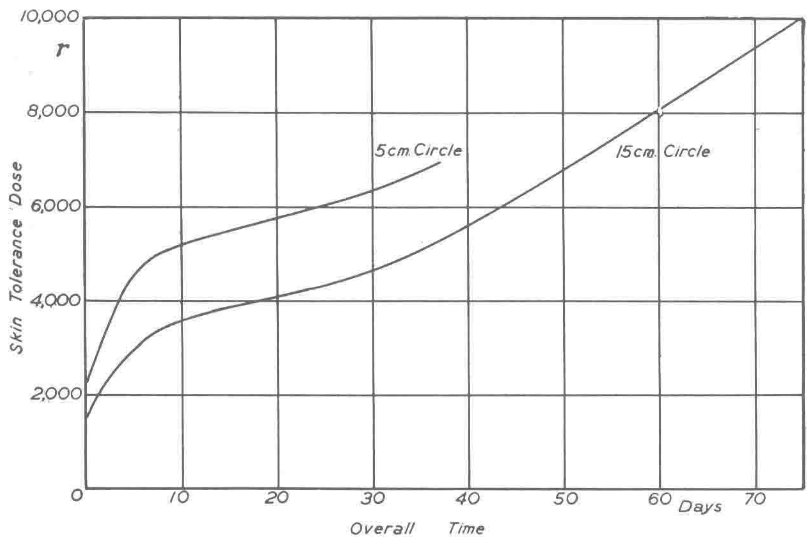

FIG. 1. 4.—GRAPH SHOWING RELATIONSHIP BETWEEN TIME AND THE DOSE WHICH MAY BE RECKONED AS AVERAGE SKIN TOLERANCE OF SKIN IRRADIATED BY 5 AND 15 CM. CIRCLE APPLICATORS (daily exposures at about 50 r/min. dosage rate and wave-length of half-value layer 1·5 mm. cu.).

The same relationship is probably true for tumour tissue, and the tumour lethal dose for squamous carcinoma is, for X-rays, of the order shown in the table in Chapter 3 giving approximate TLD levels. These might be considered as approximately equivalent doses from a biological point of view (that is, equal " biological " doses).

Possible Advantages of Prolonged Overall Time. Many workers believe that clinical advantage is obtained by increasing the overall time of a course of radiation. This is the reason for Regaud's use of treatment periods of from seven to twelve days for implantation techniques—a method which is now widely accepted in preference to exposures of from one to twenty-four hours as previously used. In X-ray therapy it is the basis for modern prolonged fractionated therapy, particularly in relation to malignant disease of the mouth and throat. This employs treatment periods of from three weeks to three months.

These views on the advantage of prolonged treatment are not universally accepted. Wintz of Erlangen maintains the contrary that the ideal overall time is the shortest within which a lethal dose can be given without producing undue systemic effects. His view might be expressed as an opinion that therapeutic ratio is optimum when time is short.

I have found it difficult so far to fit my experience completely to either theory, but am in favour of interpreting experience as indicating an appreciable advantage from prolonging exposure time. Nevertheless, there are many circumstances in which the more obvious advantages of a short period of treatment justify its use. This is true, for instance, in the treatment of small lesions, in the treatment of aged persons, in palliative therapy, and in dealing with tumours where the therapeutic ratio is high and some latitude is in consequence permitted. On the other hand, one's own impression, taken along with the widespread belief that prolongation of radiation has advantages justifies acceptance of the working premise that a prolonged overall time factor provides the optimum technique and is therefore essential in curative therapy where the volume of the tumour is not very small, or where the therapeutic ratio is low.

Fractionation. The most important element of the time factor is overall time, that is, the time from the beginning of a course of radiation until its completion. The question of fractionation, however, also arises, more particularly in regard to X-ray treatment, which is of necessity discontinuous. Experimentally it has been shown that radiation delivered intermittently at any dosage rate per exposure over any period produces the same skin effect as follows continuous irradiation at low dose rate to the same total dose over that same period, provided that the former dose is adequately fractionated. Opinion differs as to what constitutes " adequate " fractionation in this sense. For periods of seven or more days radiation once daily is near enough to adequate fractionation for all practical purposes ; for periods of two to five weeks' radiation every second day is probably nearly equivalent to continuous irradiation, but even so it is still preferable to employ daily exposures. In the actual working of a department, the need to interrupt treatment over the week-end also arises and for overall periods of two or more weeks, treatment can be omitted on Saturday and Sunday without altering the effect of a total given dose over any overall period of treatment.