SUPER-VOLTAGE X-RAY THERAPY

RALPH PHILLIPS

Supervoltage X-ray Therapy

A Report for the years 1937–1942 on

The Mozelle Sassoon Supervoltage X-ray Therapy Department, St. Bartholomew's Hospital

by

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FOREWORD

In the text of this little book Mr. Phillips reminds us that if we assume that the results of X-ray therapy in cancer depend mainly upon the physical dose administered to, or perhaps, more accurately, absorbed by, the neoplasm, then all our physical knowledge of this remedy suggests that the "supervoltage" method promises better results than mere "deep" X-rays. This was the *a priori* reason for deciding that a good trial should be given to a high voltage application of X-rays and the argument amply justified the painstaking research, and the carrying of this thesis into practice, which were undertaken by Mr. Phillips and his colleagues at St. Bartholomew's.

The decision to proceed with the trial of a million volt X-ray apparatus was a bold one and the enterprise which the trial involved on the part of the team of workers engaged upon it calls for admiration.

The author's claim that the publication of this account of the trial "may have some value for comparative and historical purposes" will probably be regarded as too modest by those who follow closely the slow yet hopeful development of the principle of irradiation as applied to the treatment of cancer. It can do nothing but good to put on record a carefully documented account of this important chapter in the progress of the method.

The trial fulfilled the desiderata of any such effort to test the possibilities of a therapeutic method: it must be thorough and must be taken to the limits of success or failure. The forbearance exercised by the author of the present record in assessing the results of this piece of team work deserves a note of approbation.

Whether the therapy of the future in this field lies with "supervoltage" X-rays, or with the cyclotron or betatron, or with some other improvisation of the physical potential, we cannot say. But we can say that this record of a chapter of definite achievement has been well worth while.

HORDER

PREFACE

THIS book is no more than an interim report on an investigation into the value of supervoltage X-ray therapy, and its publication at the present time is due to the feeling that such information as it contains should be available to those making plans for the establishment of a national cancer service and for the equipment of regional radiotherapeutic centres. It takes many years for an individual or for an institution to collect sufficient data for the statistical evaluation of any form of cancer therapy, for the necessary classification according to the site of origin of the malignant neoplasm, the extent of its spread locally and by metastasization, and its morphological and histological characters, requires a large number of cases, and such cases then have to be observed for at least a five-year period following treatment; meanwhile, whatever information of value there may be in the incomplete data is withheld from the general body of medical knowledge. Secondly, the rapid advances in pure and applied physics render it probable that still more powerful apparatus will be available for radiotherapeutic research after the war, and as it is believed that the million-volt X-ray apparatus at St. Bartholomew's Hospital is the only one in therapeutic use outside the United States of America, the publication of this account may have some value for comparative and historical purposes.

The temptation to expand a record of observations into a monograph on supervoltage X-ray therapy has been resisted, for a critical assessment of its value is not yet possible; inevitably, however, ideas culled from American writers and British colleagues will be found incorporated in this report without due acknowledgment of their source. It thus becomes almost invidious to mention others by name, but I must acknowledge my indebtedness to the late Dr. Canti for the labour he expended in the planning of the installation; to Drs. Finzi, Donaldson, Levitt and Scowen, and to Prof. Hopwood for continuous assistance, and to all my colleagues at St. Bartholomew's Hospital for their co-operation in the treatment of their patients; to Prof. Mayneord for reading through the draft report and making many valuable

suggestions and alterations; to Dr. Allibone and his staff in the High Voltage Research Department of Messrs. Metropolitan-Vickers Electrical Co. Ltd. for their fertility in ideas and their skill and ingenuity in design; to Mr. T. Smith, F.R.S., who designed the periscopic mirror system; to many commercial firms who have ungrudgingly contributed of their knowledge and skill; and to Dr. Bernard Halley Stewart for his unfailing interest and encouragement. Lastly, I should like to express the hope that this example of the co-operation of the research facilities of a manufacturing firm with a voluntary hospital may lead to still further developments in the post-war years, thus avoiding such economic difficulties as might delay the equipment of radiotherapeutic centres if they were dependent upon foreign manufacturers.

RALPH PHILLIPS

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SUPERVOLTAGE X-RAY THERAPY

I

THE DEVELOPMENT OF RADIOTHERAPY AT ST. BARTHOLOMEW'S HOSPITAL

X-rays and radium were in use for the treatment of patients at St. Bartholomew's Hospital from the beginning of this century, but it was not until 1919 that an organised investigation into their application and effects was begun under the direction of a specially appointed Radium Committee. In that year a quantity of radium which had been used in gun-sights and other instruments during the First World War was given by the Government to the Medical Research Council, who then loaned it to various hospitals and institutions for medical and scientific purposes. The Radium Committee at St. Bartholomew's, realising that the clinical use of radiations must be based on exact scientific knowledge of their nature and biological effects, took a wide view of its functions, and has from the beginning initiated and supported experimental research as well as organising a radiotherapeutic service. Thus its stimulating influence has been felt both in the Hospital by reason of its continuous investigations into the treatment of cancer and other diseases, and also in the Medical College by reason of its support of research in a subject which has been the growing-point of science for the past half-century. Some of the results of its work have attained international recognition, such as the Canti cinematographic demonstration of the effects of radium on the living cell, the Finzi-Harmer fenestration operation for the radium treatment of cancer of the larynx, and the Keynes technique for the interstitial radium needling of cancer of the breast. While its researches have always been planned with a view to the medical application of their results, the wide field over which they have ranged is illustrated by a selection of the problems investigated: the polymerisation of liquids by γ-rays and neutrons (Hopwood), the normal limits of the white blood cell count and the effects of radiation on the blood (Simpson), the demonstration of lymphatic embolism as a normal method of cancer spread (Gray), the behaviour of viruses in tissue-culture (Bland), the demonstration of nuclear bodies in bacteria (Robinow), the anatomy of the tracheo-bronchial lymph glands (Nelson), precancerous changes in the stomach (Magnus), the prognostic value of the histological grading of tumours (Phillips), the growth of transplanted human tissues in the anterior chamber of the rabbit's eye (Scowen).

In 1921, following a visit of the Radium Committee to Erlangen, it was decided to investigate the value in the treatment of cancer of the new "deep therapy" (200 kv.) X-ray apparatus. But the Hospital's finances were fully extended in reconstructing its eighteenth century buildings and in erecting new surgical and medical ward blocks, so that it was not until 1924 (the necessary funds having been collected privately by Donaldson) that the deep X-ray apparatus was installed. At this time the ever-widening scope of the Radium Committee's work required a change of name to Radiotherapeutic Research Committee. A few years later, in 1928, it absorbed another committee—the Lead Research Committee, which had been specially appointed to investigate Blair Bell's work—to become the Cancer Research Committee under the chairmanship of Sir Thomas (now Lord) Horder. This Committee soon became responsible for the organisation of a modern cancer service, and in 1934 it was raised to the status of a Cancer Department.

The new deep therapy research, under the able guidance of Finzi and Levitt, justified itself from the beginning, and when the first statistical assessment of its value was made in 1929, the results were seen to be so superior to those of the less powerful apparatus previously in use that it seemed very desirable to foster the development and investigate the value of still more powerful apparatus. While financial support for the continual development of the work of the Radium Committee and its successors had always been forthcoming from many sources, and particularly from the annual grants of the British Empire Cancer Campaign, both the capital cost and the running expenses of a supervoltage X-ray therapy apparatus appeared to be beyond its resources when first projected in 1931. But it was not long before the far-seeing generosity of Mrs. Meyer Sassoon made it possible to initiate the necessary development work on the apparatus and a building to house it, while the Sir Halley Stewart Trust ensured its running by granting a five-year Fellowship to the radiotherapist entrusted with the work.

The Mozelle Sassoon Supervoltage X-ray Therapy Department was formally opened by its donor, Mrs. Meyer Sassoon, on 10th December, 1936, in the presence of Lord Rutherford, Lord Stanmore, Lord Horder, Dr. Bernard Halley Stewart and a distinguished assembly. Six months later the treatment of patients was begun at 700 kv., and two years later at 1,000 kv., at which voltage the apparatus has given uninterrupted service for the past five years. Its running has been occasionally interrupted for a day or two after some of the heavier air-raids on London, owing to failure of electricity or water supplies, but the Department has been fortunate in escaping damage, particularly when a 750-lb. bomb fell only ten yards away but failed to explode. On another occasion a piece of the outside roadway was projected through the roof of the Department and the jagged end of the wire reinforcement punctured one of the oil-immersed condensers, and the general concussion of heavy bombs usually broke some of the vacuum seals; but these minor effects of air-raids never caused any interruption in the treatment of patients.

II

THE POSITION OF X-RAY THERAPY IN THE YEAR 1935

Until about 1915 the maximum voltage of an X-ray apparatus was about 150 kv., but after the First World War the production of apparatus running at 170–200 kv. gave rise to "deep" X-ray therapy. The penetrating power of X-rays increases as the voltage is raised, so that the term "deep X-ray therapy" was a convenient way of expressing at that time that it was then possible to deliver an adequate dose of radiation to a tumour situated some distance beneath the surface of the body. When further technical advances made feasible apparatus running at 500 kv. or more, a new term was required to distinguish it from the by then standardised 200 kv. apparatus, and so "supervoltage" was introduced. These descriptive terms—"superficial" therapy for voltages up to 130 kv., "deep" therapy for the 200–400 kv. range, and "supervoltage" therapy for 500 kv. upwards—have little to recommend them except brevity, but are in general use at the present time.

The first attempt to increase the operating voltage of vacuum tubes above 200 kv. was made by Coolidge in 1925, when he constructed a sealed-off tube which operated at 300 kv. In 1927 Allibone constructed a similar electron tube which operated at 400 kv., but this tube was continuously evacuated, first by mercury pumps, and then in 1928 by oil-diffusion pumps, using the new low vapour-pressure Apiezon oils discovered by Burch. The principle of continuous evacuation marked an important step forward, as it overcame the difficulties of applying high voltages to sealed-off glass vacuum tubes with their constant liability to puncture, and permitted increased flexibility of design and great reduction in maintenance costs. Its earlier application was delayed on account of the expense of the liquid air required as a refrigerant for the mercury vapour pumps, so that the discovery of Apiezon oil was the starting point for subsequent developments.

By 1933 Allibone and his associates in the High Voltage Research Laboratory of the Metropolitan-Vickers Electrical Co. Ltd., had put the production of continuously evacuated X-ray tubes for

250 kv. on a commercial basis, and were confident that a tube of similar design could be built for 1,000 kv. There were at that time very few supervoltage tubes in operation: the Lauritsen multi-section type at Pasadena had attained over 1,000 kv., but did not appear sufficiently reliable for continuous clinical work; the Coolidge cascade type in the New York Memorial Hospital was run for a time at 700 kv., but was similarly unreliable; the two largest European manufacturers of X-ray apparatus—Siemens and Philips—had not succeeded in making X-ray tubes which would withstand more than 500 kv. and 400 kv. respectively. Furthermore, none of the existing designs appeared likely to satisfy essential requirements such as constant potential and an X-ray beam which could be utilised at varying angles. Allibone's proposals afforded other desirable features such as a short focus-skin distance and a filament-changing device, and a guaranteed minimum operation of 600 kv. and 3 ma. Since the flexibility of design gave reasonable certainty of 1,000 kv. being obtained, a contract was signed early in 1934 for the design and manufacture to be put in hand, and plans for housing the installation were begun.

The developments in supervoltage design since 1935 have been rapid, but there has been no cause for regretting the choice of the Metrovick constant potential continuously-evacuated equipment. The impulse generator of Brasch and Lange has several disadvantages and has not yet been successfully applied to an X-ray tube; the Sloan high-frequency generator does not permit much flexibility in treatment, and the same criticism might be applied to the van de Graaff electrostatic generator; the low-frequency resonant transformer and multi-stage tube unit of Coolidge, operating in Freon, has the great advantage of compactness, and may become the standard 1,000 kv. equipment after the war; while for the higher voltages of 20 million volts or more the Kerst betatron is the most likely development.

THE PHYSICAL VARIABLES IN X-RAY THERAPY.

The physical factors which can be varied in radiotherapy are the wave-length of the radiation, its penetration and absorption in the tissues, the dosage-rate, the time-interval between successive doses, and the overall time—days or weeks—of the series of doses constituting the complete treatment. The physical and chemical effects of variations in these factors are seldom amenable to mathematical analysis, while the powers of adaptability, change and recovery inherent in living cells render impossible any theoretical prediction of biological effects. Thus knowledge of radiotherapy is largely empirical, although it has been possible to build certain useful theories on the basis of the observed effects.

Observations have shown that the effects of the same dose of radiation on different animals, organs, tissues or cells are different. Those which are relatively more damaged are said to be more radiosensitive, and the radiation is said to have a selective action.

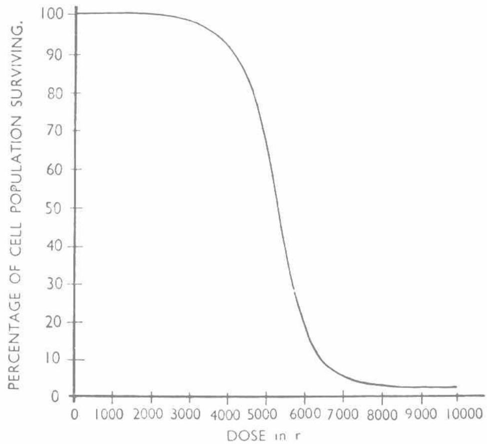

FIG. 1.—Sigmoid Survival Curve

In general, malignant tissues are more radiosensitive than normal tissues, and this difference constitutes the basis of radiotherapy in cancer. But there are many exceptions to the so-called "Law" of Bergonié and Tribondeau that the radiosensitivity of cells is directly proportional to their reproductive activity and inversely proportional to their degree of differentiation, so that no general theory of radiosensitivity can yet be formulated.

It is generally assumed that the biological effects of X-rays are due to changes in some of the cells irradiated. In the successful treatment of a malignant neoplasm by radiotherapy, it is, however, unlikely that every cancer cell is destroyed by the direct action of the radiation, for experimentally the lethal effect of radiation on most biological populations is represented by a sigmoid survival curve (Figure 1). It would thus appear that below a certain threshold of dose, no cancer cells are destroyed; between certain fairly narrow limits of dose, the bulk of the cell population is killed; but even with the maximum possible dose, there will still be a few cancer cells surviving. In the successful case, therefore, the potential activity of these surviving, though probably damaged, cancer cells must be overcome by the tissues in which they are lying. Effects of radiation on these normal tissues or "tumour bed," such as reduction of the blood-supply and promotion of fibrosis, are referred to as the indirect effects of radiotherapy. It will be noted that both the direct effect on the malignant cells and the indirect effects on the tumour bed are localised to the region irradiated, but there may also be a third type of effect dependent upon more generalised changes in bodily metabolism; as the volume irradiated approaches an appreciable fraction of the total volume, the quantity of radiant energy absorbed in the body as a whole appears to play an increasingly important part in the effects produced.

The action of radiation on the cell is primarily exerted on the nucleus, and thereby on the cell processes which control growth. The effect of doses of the order used in radiotherapy is a specific injury to the nuclei of potentially dividing cells, and is a graded one, ranging from a completely reversible inhibition of growth to an injury that results in the death of the cell.

These biological effects of radiation are as yet only loosely correlated with the clinical results of radiotherapy, so that the main comparison between supervoltage and deep X-rays must be based on such clinical data. But some comparison is also possible between physical factors, for which the following summary of the views held in 1935 will serve as a basis.

1. *Wave-length.*

The wave-length of an X-ray beam depends upon the voltage at which the rays are generated; the higher the voltage, the shorter the wave-length, and the greater the quantum energy. According to physical theory, the effects of X-rays are directly proportional to the amount of energy absorbed, and should therefore be independent of wave-length. While some biological experiments show that effects may differ over as much as a five-fold range according to the wave-length used, there is much contradictory evidence, and clinical observations likewise show no agreement in the correlation of the results of treatment with the wave-length employed. The contradictions may arise in part from the fact that the unit (roentgen or "r.") in which radiation dosage is measured is based on the amount of energy absorbed from an X-ray beam in air, and is thus by definition independent of wave-length, and so takes no account of the energy absorption from different sized quanta in biological materials of varying atomic composition.

X-rays used in therapy occupy only a small part of the electromagnetic spectrum, their wave-length range being approximately from 10^{-8} to 10^{-10} cm., i.e. from 1·0 to 0·01 Å.U. Of shorter wave-length are the gamma-rays of radium, while on their longer side are the Grenz rays and then the ultraviolet with a wave-length of some 3,000 Å.U. The general properties of the electromagnetic spectrum do of course vary markedly with wave-length—wireless waves, heat, light, ultraviolet, X-rays—so that on a priori grounds smaller variations might be expected in each group according to their individual wave-lengths. Just as the biological effects of red light differ from those of violet light, so those of X-rays of 1·0 Å.U. might be a little different from those of 0·01 Å.U.; but whereas the former difference can be consciously appreciated, the latter—if it exists—can only be determined by experimental observations on suitable material.

2. *Penetrating Power.*

The shorter the wave-length of an X-ray beam, the greater is its penetrating power, so that the problem often encountered in deep X-ray therapy of delivering an adequate dose to a deeply-situated tumour might be more easily solved by the use of supervoltage X-rays.

3. *Absorption in the Tissues.*

Physically the absorption of X-rays is regarded as occurring by the transference of the energy of the X-ray beam to the electrons of the absorbing matter, and the kinetic energy thus imparted to the electrons appears finally as chemical change or as heat. There is, however, a wide and unbridged gap between this physical concept and the biological effects of such absorption in tissues, for here unmeasurable temporal and spatial factors are of at least as much importance as the quantitative. It is not possible either to measure or to calculate the actual energy absorption in tissues, but the dose in roentgens can be found by measuring the energy absorption in a small mass of air placed at the desired point, and in this way the doses of radiation at different points in the tissues and under different conditions can be compared.

The dose of radiation at a point within the body is usually less than that on the surface, from the operation of the inverse square law diminishing the intensity of the X-ray beam the further it travels from its source, and from the progressive attenuation of the beam as it passes through the tissues. The relationship between the dose at a depth and the dose at the surface is called the "percentage depth dose" (P.D.D.), and it varies with the wave-length of the X-ray beam, with its cross-sectional area ("field-size"), with the focus-skin-distance (F.S.D.), and with the absorbing power of the tissues. A complex measurement depending upon so many factors cannot be calculated, but its determination is indispensable to the planning of a patient's treatment; the P.D.D. would be expected to increase with decrease in wave-length, so that supervoltage X-rays should have an advantage over deep X-rays in this respect.

4. *Dosage-rate.*

The dosage-rate of an X-ray beam, often but inaccurately called its intensity, is expressed in the number of roentgens recorded per minute by the measuring instrument. It varies directly with the current passing through the X-ray tube (milliamperage), and increases rapidly in a complex manner as the tube voltage is increased; a supervoltage tube should therefore be a more efficient source of X-rays than a deep therapy tube, but the extent of this gain can only be determined by measurement.

A dose of X-rays is given by the product of the dosage-rate and the time of exposure. In physics a given dose may be expected constantly to produce the same effect, but this is not the case in biology; here the effect produced may vary with the time in which the given dose is admininstered, since the recovery rate of the biological object affects the result. In general, a high dosage-rate produces a greater effect than a low one, since there is less time for the recovery processes to operate.

The differing rates of recovery from injury exhibited by different tissues and cells afford the possibility of different dosage-rates having a varying selective effect. The so-called Coutard method of protracted X-ray therapy is based on the supposition that normal tissues are less injured by a given dose of X-rays administered at a low dosage-rate than at a high one, but that malignant tissues do not show any such difference over the range examined (from about 3 r./min. to 50 r./min.). There may well be an optimum dosage-rate for each type of cancer, so that in a comparison of the effects of supervoltage with those of deep X-rays it is desirable to avoid variations in the dosage-rate.

5. *Time Interval between Successive Doses.*

The prescribed dose of X-rays may be given in a single exposure, as in the original Erlangen or "massive single dose" method. Although still used by Wintz, this method has in general been abandoned except for small superficial neoplasms, on account of the high incidence of X-ray sickness and other undesirable effects.

When the prescribed dose is to be given in a number of exposures, the method is called the "fractionated dose method." The time interval between successive doses may be from a few hours up to 72 hours, but is in general 24 hours; the size of each dose may be varied, but is usually kept the same throughout the course of treatment. The aim of the method is to summate successive doses in the malignant tissue without exceeding the tolerance of the normal tissues, and it is based on the observation that the recovery rate of malignant tissue tends to be slower than that of normal tissue.

6. *Overall Time of Treatment.*

The period over which a course of X-ray therapy extends may vary from a few days to many weeks, depending in part upon the size of each fractional dose and on the time interval between successive doses, but is in general from three to five weeks. The same consideration of the varying recuperative powers of different tissues is exploited so as to obtain the maximum selective action of the radiation on the malignant tissue.

The Effects of Physical Variables on Clinical Results.

The physical variables in X-ray therapy are seen to be many and complex, and offer scope for wide variations in methods and technique, while the empirical determination of the optimum con-