CANCER

EDITED BY

R.W. RAVEN

VOLUME

5

# CANCER

*Edited by*

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RADIOTHERAPY

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PART IX

# RADIOTHERAPY

## NOTE ON TERMINOLOGY

X-RAYS used in the treatment of malignant disease range from about 60 kv to 95 kv ("low-voltage" or "superficial" x-rays) for superficial lesions such as basal-cell carcinoma, from 100 to 140 kv ("medium-voltage" x-rays) for slightly deeper lesions such as subcutaneous recurrence from carcinoma of the breast, and from 200 to about 500 kv (usually 200 to 250 kv) ("high-voltage" or "deep" x-rays) for deep-seated lesions. More recently, super-voltage x-rays in the range 800 kv and upwards have been used in clinical and experimental work. At the present time super-voltage irradiation for the routine treatment of cancer implies the use of x-rays generated at 1–8 million volts or *gamma*-rays from artificial radioactive isotopes such as cobalt 60 (telecurie therapy). In this volume the terms low-voltage, medium-voltage, high-voltage and super-voltage, in addition to cobalt 60 (telecurie therapy), are used.

Two units of dose in use at present are roentgens and rads. They are nearly equivalent and in the range of x-rays commonly used 96 rads = 100 roentgens (r).

In references to x-ray tube potentials the following abbreviations are used:

| | |
|---|---|
| v | volt |
| kv | kilovolt (thousands) |
| MV | megavolt (millions) |

In references to the photon energies of x-rays and *gamma*-rays, the following abbreviations are used:

| | |
|---|---|
| kev | kilo-electron volt |
| Mev | mega-electron volt |

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## CHAPTER 1

# HISTORICAL BACKGROUND OF RADIATION IN CANCER

SIDNEY RUSS

## INTRODUCTION

THE background presented to the student of physics at the end of the nineteenth century is summarized by Sir Arthur Schuster who wrote : "The seven landmarks which bring us to nearly the end of the 19th century are Newton's establishment of the Law of Gravitation, Dalton's Atomic Theory, Faraday's electrical discoveries, Young's contribution to the Wave Theory of Light, Joule's foundation of the Conservation of Energy, Kelvin's demonstration of the Dissipation of Energy and Maxwell's formulation of the Electromagnetic Theory of Light."

This gives the impression that however the background may change these sign-posts must remain. Yet in the first half of the present century, at least three of these outstanding contributions to scientific knowledge have been challenged in the sense that their seeming completeness is open to question. This came about through the discoveries of Einstein, Rutherford and Planck.

The works of Faraday and Maxwell are most relevant to the subject of radiation in cancer. Faraday studied the discharge of electricity through gases and concluded that besides the solid, liquid and gaseous states, there was a fourth state for which he suggested the name "radiant matter". This prophecy was fulfilled when Thomson (1897) discovered the electron.* Faraday was followed in these studies by many physicists in Great Britain and other countries, notably by Crookes, Lodge, Lennard and Hittorff, and much delicate and detailed work was carried out in describing the visual appearances when an electrical discharge passes through a rarefied gas.

Maxwell (1873) had convinced physicists that light, ultra-violet radiation and radiant heat were all manifestations of an electromagnetic nature and, on the basis of the theory that bears his name, had predicted the existence of radiation with a lower frequency than radiant heat. Such radiation was discovered by Hertz (1888), 9 years after Maxwell's death. The term "Hertzian Waves" gradually gave way to "Wireless"

## HISTORICAL DATA

### *Roentgen rays*

On November 8, 1895, Roentgen discovered a new kind of rays. He communicated this discovery of Eine neue Art von Stràhlen to the *Sitzungsberichte der Physikalisch-Medizinischen Gesellschaft* in Würzburg on December 28, 1895, and a full

* The word "electron" had been used in 1891 to indicate that some purely electrical element was necessary to elucidate certain spectroscopic effects, and when Thomson isolated the "negative corpuscles" Stoney suggested that they should be called electrons and the name was applied forthwith.

translation of Roentgen's paper was published in *Nature* on January 23, 1896. The reactions of the medical and scientific world were immediate but necessarily different in nature. To the medical world a new insight in the strict sense of the word was put at its service, to the physicist a challenge as to the nature of the new rays.

Roentgen speculated upon the physical nature of his "x-rays" and ventured the opinion that they were longitudinal vibrations in the ether. Seventeen years later, however, Laue proved that they were of the same electromagnetic character as light. During this time a vast science had been developing.

In 1896 Becquerel discovered the radioactivity of uranium and in the following year Thomson discovered the electron. In 1900 Pierre and Marie Curie isolated radium from the mineral pitchblende and in the same year Rutherford discovered thorium emanation. He showed that this emanation was an unstable radioactive gas and that it gradually disintegrated to form a solid "active deposit" which was itself radioactive. Subsequently it was found that radium and actinium also produced emanations. These gases were renamed thoron, radon and actinon in 1911.

The discovery of the electron following so closely upon that of x-rays might have meant an influx of physicists to the laboratories of either discoverer but Roentgen's interest in x-rays was not sustained, and less than two years after his discovery he went back to research in general physics, leaving Thomson, at Cambridge, to draw the young physicists from all over the world. In a comparatively few years the foundations were laid of our knowledge of the processes of ionization, the recombination of ions, ionization by collision, thermionics, and the general physical properties of x-rays, and particularly the outstanding work of Barkla on the recognition of "characteristic" secondary x-rays which were to have an important bearing on advances in medical radiology.

### *Thorium emanation*

By his discovery of thorium emanation Rutherford leapt into the commanding position he held in radioactivity until he died, in 1937. With Soddy he formulated the "Disintegration Theory of Radioactivity" (Rutherford and Soddy, 1904). Whereas this theory was hailed with delight by physicists, its reception by chemists was not so warm for they were told that in radioactivity Nature presented a strange contrast to the orderly state of atomic stability. A species of atom could exist with a quasi stability; atoms did not necessarily last for all time, but could spontaneously change into different ones which might or might not have stability; such were the radioactive atoms. The feature of instability was, until 1934, insisted upon by physicists as being essentially a spontaneous characteristic; it could not apparently be induced or accelerated or modified by any chemical or physical agent.

### *Experiments with* alpha *particles*

In 1907 Rutherford began experiments on the counting of *alpha* particles by means of the scintillations they produce on hitting a fluorescent screen; each hit is signalled by a minute flash of the crystal; the eye has to be accommodated for counting. Ably seconded by Geiger (who designed the counter that bears his name) the number of *alpha* particles spontaneously emitted by 1 gramme of radium was determined and the particles were subsequently identified as helium nuclei.

Rutherford used the *alpha* particles as atomic projectiles to penetrate into the interior of other atoms. In 1919 he succeeded in producing the first artificial disintegration of the atom by projecting a stream of *alpha* particles into gaseous nitrogen: he found that particles were formed which could cause scintillations at a much greater range than that reached by *alpha* particles. A hydrogen atom had been expelled from a nitrogen atom and this atom having engulfed the *alpha* particle was changed into oxygen, but it was not radioactive.

***Planck's quantum theory***

At the beginning of this century it was generally considered that when a body was emitting or absorbing radiation there was no limit to the smallness of the quantity of radiation which could exist, but by the study of thermal radiation Planck (1900) outlined his views about the nature of radiation and made the suggestion that when a body emits radiation it does so in definite units of radiant energy. He supposed that the radiation from any atomic oscillator, though having a definite amount of energy, nevertheless spreads throughout space like a spherical electromagnetic wave. Einstein, however, considered that the dominant feature of this new conception was the particulate idea of localized energy and the name "photon" was used to express this quantity or quantum. The term quantum became linked with the name of Planck. The quantum associated with any particular radiation depends upon the frequency and is given by the product $hn$, where $h$ is a constant known as Planck's constant and has the value $6{\cdot}545 \times 10^{-27}$ erg seconds, the product of $h$ and $n$ being ergs.

There is a dual conception involved, for it is not only a minimum quantity intrinsic to the radiation process, but also to the absorption of such radiation by matter, and this was one of Einstein's contributions to Planck's original theory. As a first application, Einstein predicted a relationship between the energy of electrons liberated by a photo-electric action and the frequency of the exciting radiation; this was later verified experimentally.

How are we to conceive what goes on in the passage of radiation from a point A to a point B? Newton visualized a stream of corpuscles, Huygens thought in terms of wave motion, and waves were certainly needed when it was found that two beams of light originating from the same source could interfere with one another so completely that their coalescence meant extinction—one can see such interference in water waves. Maxwell then eliminated all mechanical attributes by his imaginative excursion into electromagnetism. So long as periodicity prevailed, as in ordinary wave motion, he found no difficulty in explaining optical interference, polarization, double refraction, selective reflection and so on. Nevertheless, it was still generally thought or inferred that radiation from as weak a source as a candle flame would extend indefinitely into space, only getting weaker but still present. No one probably believed this but they saw no answer to the question: If it stops, what is there to stop it? If Planck's quantum ideas put an end to this sort of speculation, they also had to come into the mental picture, superimposed in some way upon what was already there. No greater mistake could be made than to suppose that Planck had overthrown Maxwell; the ideas of both are supplementary.

If there are corpuscles or quanta and yet something wave-like about radiation, Thomson (1897) could visualize a spotted wave front like a fisherman's net on the water, the quanta being thus linked with the waves, but the imagination is strained for many in seeing how the magnitude of the quanta accommodates itself to the wavelength that carries it, a further difficulty being that with the diminishing wavelength (harder and harder x-rays) the quanta get bigger and bigger. If on top of their picture is superimposed, as there must be, an electromagnetic periodicity, there is indeed plenty to engage the mind.

***Atomi structure***

About 1910 Rutherford was being led to the view that the essential feature of atomic structure was that the main mass of an atom was concentrated about a central positively charged nucleus with electrons spatially distributed about it. He was joined by Bohr who, attracted by many features of the quantum theory, attempted to combine the structural ideas of Rutherford with the dynamic ones of Planck. In this way was evolved the Rutherford-Bohr plan of atomic structure.

It is significant to recall that Barkla made his discovery of "characteristic" secondary x-ray by the aid of the simple Equation (1) and that Rutherford and Soddy developed their "Disintegration Theory of Radioactivity" on the experimental basis of Equation (2):

$$\text{Equation (1)} \quad I = I_o e^{-\mu x}$$
$$\text{Equation (2)} \quad Q = Q_o e^{-\lambda t}$$

These equations are identical in form, yet they represent different phenomena. The first expresses the way in which a homogeneous beam is absorbed by a homogeneous medium and was in use in optics long before x-rays were discovered. It expresses briefly the fact that if a homogeneous medium of thickness X absorbs say Y per cent of the radiation incident upon it, then the next thickness X will absorb Y per cent of the radiation incident upon it and so on *ad infinitum*. It may be called an inevitable or common-sense law.

In 1914 Mosely investigated the characteristic x-rays emitted by a larger number of elements. It is impossible to exaggerate the classic distinction and the far-reaching implications of his results. He showed that every element from chromium to gold is characterized by an integer N which determines its characteristic x-ray spectrum. Every detail in such a spectrum can be predicted from the spectra of its neighbours. The integer N, which he called the atomic number, is identified with the number of positive units of electricity contained in the atomic nucleus (Rutherford-Bohr model).

Equation (2) expresses the mode of decay of all radioactive substances. If half of such a substance decays in time T, then half of the remainder takes exactly this time to decay to half its value, but in this case it is not *ad infinitum*.

So far from being a common-sense law, it remains, after 50 years of radioactive study, an inscrutable law. Can we imagine the process by which, in an enormous assembly of similar atoms, exactly the same fraction of the atoms present at any moment is going to be transformed? We are reminded that in any radioactive manipulations we are nearly always dealing with very large numbers. If we begin measurements with a millicurie of radon we are dealing with about 20 million million molecules. In about 150 days we should be dealing with only about 20. Does the law still hold? This has been tested, and the simple exponential law did not hold. The exponential law of decay is simply the statistical expression of what happens to a large assembly of unstable elements. These two equations form the basis of measurements in physics at the service of medical radiology.

## ARTIFICIAL RADIOACTIVITY

In 1934 Joliot and Curie (daughter of Madame Curie) discovered a way of making an element radioactive. They exposed boron to a stream of *alpha* particles; some nitrogen was produced, which was radioactive and changed into carbon.

### *Radioactive isotopes*

This discovery began a second era in radioactivity and the new substances were called radioactive isotopes. The term isotope, coined by Soddy, means "the same place in the periodic table of elements". There is ordinary nitrogen and also an isotope of it which is radioactive; they have exactly the same chemical properties. The work done by physicists, especially by Fermi, can be gauged from the fact that in a comparatively few years all the known elements were shown to be susceptible; they could all be made radioactive.

It was discovered also that by suitable atomic treatment entirely new elements could be formed of which plutonium is a notable example.

### *Cobalt and caesium*

Radioactive isotopes are nearly all *beta*-ray emitters, with "time to half value" ranging from a few hours to about 1,000 years ($^{14}C$), but two important ones emit *gamma* radiation also. These are cobalt and caesium and are available in large quantities. Thirty years ago radium began to be used in units of 5 or 10 grammes as *gamma*-ray sources, to be applied externally in a similar manner to x-rays; but with these quantities the output did not compare favourably with that of high-voltage x-ray tubes. The advent of cobalt and caesium may not only replace the gramme units of radium but may revolutionize the technique of radiotherapy, especially that of the past 10–15 years, with the million volt plant. An adequate interval may not have elapsed for an evaluation of the very high-voltage technique in the treatment of cancer, especially that of deep-seated tumours. There have been dissentient voices raised, for it is recognized that in the passage of very short-wavelength radiation through the body the tissues are made radioactive. If very penetrating radiation is proved to be advantageous, then a consideration of cost wiil be the chief factor in deciding upon a change-over to the man-made radioactive sources. As an indication of the present strength of cobalt or caesium units one has to get used to such values as 2,000 curies.

### *Radio-iodine*

So great has been the activity among the producers of radio-isotopes that more than a thousand of these substances have been prepared. Their greatest use is in industrial processes, but some of them are used in the treatment of cancer, notably radio-iodine and radio-phosphorus. The earliest use of radio-iodine in the treatment of carcinoma of the thyroid was by Keston, Ball, Franz and Palmer (1942). Encouraging results have been obtained in selected cases.

*Radio-phosphorus*

Radio-phosphorus is taken up by some of the sarcomas and is, moreover, selectively absorbed by the lymphatic tissues and the marrow. Since 1936, it has been used for patients suffering from leukaemia or polycythaemia vera with results which are stated to be comparable with those from x-ray treatment.

## RADIOBIOLOGY

Biologists have studied the effects of x-rays upon living organisms. In 1899 Schaudinn carried out an investigation upon many varieties of protozoa by exposing them to x-rays at about 60 kilovolts. The chief effects observed were that those with the more fluid protoplasm were more sensitive than the others, that the polynucleated forms were more affected than the mononucleated, and the parasitic varieties were unaltered.

Perthes (1904) and Mottram (1913) showed that the ova of *Ascaris megalocephala* were excellent material for study of radiation effects. Mottram drew attention to the important fact that these ova when in mitosis were especially vulnerable to radiation and that in the metaphase they exhibited the greatest sensitiveness. Moreover, whereas no differences were observed in the appearance of the centrosomes, attraction spheres or spindle, there were profound changes in the chromatin consisting for the most part of irregular fragmentation, irregular migration of the fragments to the poles, and crowding of the granules against the cell wall.

The action of x-rays upon genes discovered by Muller (1927) opened up a subject having important bearings on human welfare.

Spear (1953) and his colleagues approached the study of cellular and tissue reactions to radiation from a preliminary basis of tissue culture and thence on to malignant tumours in bulk. They confirmed the special sensitivity of cells in mitosis and extended their observations to the action of radiation upon normal tissues and upon human malignant tumours.

Spear shed further light upon the fate of cells receiving sublethal doses of x-radiation or $\gamma$-radiation. Fortunately many examples were met in which sublethal doses could, if repeated, bring about the gradual dissolution of unwanted cells. Alternatively, it was found that certain types of malignant tumour were responsive to radiation by a process of differentiation which rendered the cells sterile and the tumour innocuous. There were cases, however, in which this did not occur and a subsequent renewal of growth occurred from the residual and differentiated cells present. On the basis of such work there emerged the hope that by a serial of biopsies of malignant tumours during x-ray or radium treatment, a useful prognosis could be made. These researches are recognized as an important part of the background of thought of practising radiotherapists.

***Effects on the generative system***

Studies designed to show the effects of radiation upon the development of the whole animal were made by Hertwig (1913). He showed that restriction of development occurred and that monstrous forms eventuated whether the ova were fertilized before or after irradiation. It was many years later that such observations were extended to man, for after Hiroshima malformed infants were born to women who had suffered irradiation.

Some of the most detailed, and in their implications, very important, experiments have been carried out upon the generative system. Bergonié and Tribondeau (1904), as a result of their observations upon the x-rayed testicle of the rat, formulated their law: "Immature cells, and cells in the active state of division, are more sensitive to the x-rays than are cells which have acquired their adult, morphological or physiological characteristics".

More has been read into this statement than is warranted. In the field of malignant disease it is true that sometimes rapidly growing tumours are sensitive to radiation and very slowly growing ones appear very resistant, but a generalization cannot be made to the extent of classifying tumour sensitivity simply in terms of rapidity of growth.

### *Action of ionizing radiations*

The nature of the action of the ionizing radiations upon living cells is still obscure. Ionizing power is the one feature which sharply distinguishes these radiations from the others forming the electromagnetic spectrum, so that almost inevitably anyone trying to formulate a theory of action of these radiations upon the living organism would fasten on this unique characteristic and explore its possibilities. One of the first theories of action came from Dessauer (1923) which did not, however, have ionization as its basis. He, no doubt influenced by quantum ideas, considered that though x-rays might be regularly distributed throughout a mass of tissue, their absorption was essentially particulate, and where it was absorbed, energy was transformed into heat at localized points in the cell with subsequent destructive effects. This was the "hot point" theory. The theory did not gain many adherents.

### *The "target theory" of Lea*

In later years, several physicists have turned their attention quantitatively to the ionization processes operating throughout irradiated tissues, particularly Lea whose "target theory" of action has merited attention (Lea, 1946). The "target" or "quantum hit" theory was modified by the postulate that there is a specially sensitive volume inside the cell within which it is necessary that ionization should be produced in order to cause biological change: ionization occurring outside this volume is assumed to be harmless. Lea pointed out that there were three different types of biological response to which his target theory had been applied. These classes of action are due (1) to a single ionization; (2) to the passage of a single ionizing particle; and (3) to the passage of a number of ionizing particles. It is in groups (1) and (2) that the theory has proved most successful.

Catcheside, Lea and Thoday (1946), in studies upon chromosome aberrations among the seeds of the grass tradescantia, forecast that there should be a sharp maximum in efficiency of chromatic breakage by soft x-rays of a wavelength between 4 and 5 Ångström; this was verified experimentally.

Lea's target theory is greatly concerned with the ion density that occurs in irradiated media. As Gray (1947) has pointed out there is a very large range of ion density met with in going from *alpha*-rays (high) to *gamma*-rays (very low) and biological response may be linked up with such phenomena. It is unlikely, however, that ion density alone can explain the multifarious reactions of living matter.

It may be that ion gradients play a part, for these too are a varied feature among types of radiation.

*Selective action*

The terms "selective action" and "differential action" have been much discussed since they were first used. "Action éléctive" was used by Regaud, Nozier and Lacassagne (1912) to denote that when a beam of x-rays passed through a mass of tissue the effects were essentially different as it passed through diverse tissue, some cells being much more affected than others. This term was translated as selective action and was sometimes used in the sense that the rays selected certain cells for undue action; this was hardly intended by the authors.

It was another matter to say that there was selective action because of some selective absorption of some constituents of a group of cells. Whatever term is used there is no doubt that the cells of the body exhibit a large range of effect under x-rays and in some cases this selective action is a favourable one in treating cancer.

Linked up with selective action, which we think of in comparative terms, is susceptibility to radiation which can be used in a more absolute sense. Man, for instance, exhibits as a whole (whole body irradiation) a degree of susceptibility which can be put at 500 roentgens for a 50 per cent mortality. Drosophila can take 20,000 roentgens for a similar mortality. This may appear unexpected, for this fly is a show piece of Nature in her mutation moods, and under irradiation conditions mutations are easily induced, yet as a whole the organism exhibits great resistance.

Whether cells exhibit a differential action under irradiation has been discussed for over 30 years. Data given by Gray (1942) showed that in producing lethal effects on the bean root, neutron radiation has eight times the efficiency of x-radiation and ten times that of *gamma*-rays. The factors are not the same for other tissues but they go the same way, that is, with an increase of ion density there is an increase in efficiency of action.

***Effects of x-rays on water***

Perhaps it is fortunate that water, being the main fluid component of the body, is not very radiosensitive and for many years it was thought that the action of x-rays on water was extremely small and unimportant.

Although recent work has confirmed that the overall effect of x-rays on *pure water* is very slight, opinion concerning *aqueous solutions* has changed in the last 15 years largely due to the work of Farmer, Stein and Weiss (1949) and Day and Stein (1949). They showed that the main action is the formation of the free radicals H and OH; a second effect yielding molecular hydrogen peroxide ($H_2O_2$) and hydrogen ($H_2$) has been demonstrated by Allen (1954). The radicals are chemically highly reactive and initiate permanent chemical changes in many different solutions.

It has been shown quantitatively that 1 rad decomposes about $6 \times 10^{-8}$ grammes of water per litre while 500 rads to the whole body give about 30 microgrammes of free radicals. The dose 500 rads is generally considered to be 50 per cent lethal to man when given to the whole body; although no one has yet been able to outline any process by which the presence of these free radicals could account for this lethal action, we must believe that intercellular and intracellular processes are in a delicate equilibrium when excess free radicals come into play.