A HANDBOOK OF RADIOTHERAPY FOR SENIOR AND POST-GRADUATE STUDENTS

by

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PREFACE

I HAVE thought for a long time that there is need for a book on radiotherapy addressed to the senior and post-graduate medical student up to, say, registrar standard. The object of such a book should be to explain, in simple non-technical language, what are the radiations used in therapy, how they are produced, how they are applied and how they produce their effects, the diseases in which they are used and the prospects of benefit from their use. This book is an attempt to fulfil that object.

I feel that some apology is due to those readers who may have some knowledge of physics for the very elementary form of Chapters I and II. These chapters are written on the assumption that the reader will have no knowledge of physics at all, for it has been my experience that a great many medical men are not only not interested in this subject, but find it positively repellent.

It is a pleasure to acknowledge my indebtedness to my friends and colleagues at St. Bartholomew's Hospital who have been so unfailingly helpful in their assistance and advice at various stages in the preparation of the book. In particular I have to acknowledge my indebtedness to Dr. N. S. Finzi, Consulting Radiologist to the Hospital, for more than twenty years my teacher, chief and friend, to whom I owe much of such knowledge as I have of radiotherapy ; to Mr. I. G. Williams, Director of the Radiotherapy Department at St. Bartholomew's Hospital, for his great kindness and patience in reading much of the manuscript and most of the proofs and for his many very helpful suggestions ; to Mr. Geoffrey Keynes and Mr. John Hosford for their most helpful advice and criticism on the chapter on Carcinoma of the Breast. Although these colleagues most kindly gave a great deal of time to the detailed reading of the typescript, they are not, of course, to be taken as necessarily endorsing all the opinions I have expressed.

To Mr. J. Jackson Richmond, my former colleague and successor in charge of the Radiotherapy Department at St. George's Hospital, I have to acknowledge my thanks for his ever-ready help in furnishing me with information about old patients to whom I wished to refer in the text, and in collecting illustrations of which Figs. 43 and 53 refer to patients treated by us during my time at St. George's and Figs. 48 and 49, refer to patients treated by him alone. To Dr. Alfred Glucksmann of the Strangeways Laboratory, Cambridge, I am

indebted for the beautiful series of micro-photographs which are depicted in Figs. 30 to 33 ; and to Dr. Arthur Jones, Deputy Director of the Radiotherapeutic Department at St. Bartholomew's Hospital, for assistance in collecting illustrations and for placing at my disposal his seemingly inexhaustible knowledge of radio-therapeutic literature. I have also to thank Mr. George Innes, Senior Physicist to St. Bartholomew's Hospital for many of the illustrations on physical and technical matters. Finally, I have to thank the publishers, Messrs. Harvey & Blythe, and in particular, their manager, Mr. R. C. Broadhurst, whose never-failing courtesy and helpfulness have greatly lightened my task ; and my secretaries, Miss Cecily Goodisson and Miss Iris Lawrence, for their part in the tedious business of typing the manuscript.

September, 1952 WALTER M. LEVITT.

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CHAPTER I

THE A.B.C. OF ATOMS AND ISOTOPES

THE ATOM may be thought of as consisting of a nucleus surrounded by a number of concentric shells or orbits. The nucleus consists of : (1) particles of matter each carrying unit positive charge called *protons* and (2) (with the sole exception of the simplest atom, the hydrogen atom) *neutrons*, identical particles of matter but without any charge.

It will simplify matters if, from the beginning, we think of the neutron as identical with a proton but without the positive charge, so that it is electrically neutral. If we think of it in this way it will be easy to follow later that a proton can change into a neutron by shedding its positive charge and also that a neutron can change into a proton by emitting a like negative charge, thus leaving it electrically unbalanced to the extent that it will have a unit positive charge, that is, it will be a proton.

The shells or orbits contain electrons in number always equivalent to the number of protons. Electrons are particles of unit negative charge, so that the charge in the nucleus is balanced by the charge in the "cytoplasm" of the atom.

The nuclear constituents are incomparably heavier than the electrons in the "cytoplasm" so that the weight of the element, our old friend the atomic weight, is accounted for substantially by the nucleus, that is the protons and neutrons. Protons and neutrons have the same mass. The sum of the numbers of neutrons and protons is known as the *mass number* and determines the atomic weight.

The identity of an element depends on the number of protons in the atomic nucleus. Thus, an element with 1 proton is always hydrogen ; an element with 82 protons is always lead and an element with 92 protons is always uranium, and their atomic numbers will respectively be 1, 82 and 92.

What is an Isotope ?

Although an element with 82 protons is always lead, the number of neutrons in a lead nucleus may vary, and, accordingly, so may the atomic weight. *Elements with the same number of protons but with varying numbers of neutrons are isotopes of the same element.* The existence of isotopes has, of course, been known for decades—

and an isotope w by definition a variety of the same element with a different atomic weight. We now know that the differing atomic weight is due to differing numbers of neutrons. The chemical and physical properties of the isotopes of an element are, generally speaking, identical.

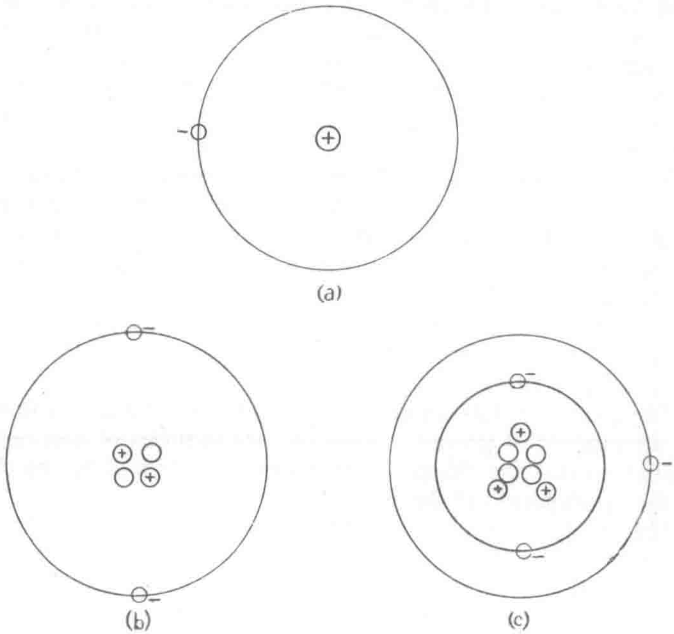


Fig. 1. The three simplest atoms. (a) The Hydrogen atom. This has 1 proton and no neutrons in the nucleus, and 1 electron in the orbit. (b) The Helium atom, with 2 protons and 2 neutrons in the nucleus, and 2 electrons in the orbit. (c) The Lithium atom, with 3 protons and 4 neutrons in the nucleus, and 3 electrons in 2 orbits.

It has been seen that the sum of the protons and neutrons in a nucleus is known as the *mass number*. Accordingly, different isotopes of the same element will have different mass numbers. The mass number is the method of indicating the particular isotope of the element, for example I^{131}, P^{32}, and so on.

Artificial Isotopes

A great many isotopic elements occur in nature. By bombarding elements with nuclear particles produced in various ways, however, at least one isotope of every known element has been produced. The simplest method of production of artificial isotopes is by forcing extra neutrons into a nucleus. Thus, sodium, with 11 protons and 12 protons, that is an atomic number of 11 and a mass number of $11 + 12 = 23$, on bombardment with neutrons turns into an isotope of sodium ; still, of course, with an atomic number of 11 (or it would not be sodium) but with an extra neutron so that it now has 13 and its mass number is $11 + 13 = 24$. Accordingly, it has now turned into Na^{24} from Na^{23}.

Radio-activity of Isotopes

Natural isotopes and some artificial ones are stable, that is to say they stay put and do not turn into anything else. Many of the artificial isotopes, however, are unstable ; that is to say they have either too many neutrons or too many protons in the nucleus to remain in equilibrium and so they readjust themselves until they finally turn into some element or isotope which is stable. They do this in various ways but the one way in which they do not do it is by emitting an offending neutron. In fact, they produce the re-adjustment by emitting other particles and radiations from the nucleus.

1. They may emit a positron. This may be thought of as clipping the positive charge off a proton whereby it turns into a neutron. Clearly, when this happens there is one proton less in the nucleus, so the element must change into the next element down the scale of atomic numbers. For example, one form of radio-phosphorus P^{30} has 15 protons and 15 neutrons but this is a very unhappy element and changes in a matter of minutes by emitting a positron from its nucleus, thus turning one of its protons into a neutron and reducing its protons from 15 to 14. It therefore becomes silicon, which is the element with 14 protons, and in this case not 15 but 16 neutrons accounting for the extra neutron which has been produced. The new element is in fact Si^{30}.

2. The second kind of particle that may be emitted from the nucleus is an electron with a like *negative* charge. These electrons (which were first observed to be emitted by radium) are known as *beta rays*, and were so named in the days before their identity was established. The effect of the abstraction of the unit negative charge is to leave a unit positive charge in a neutron. It therefore ceases to be a neutron—in other words we have produced a new proton, and the element with one extra proton is the next one *up* the scale of atomic numbers.

3. Packets of particles consisting of 2 protons and 2 neutrons may be emitted from the nucleus, thus changing the element into another element *two down* the scale of atomic numbers (by reason of the loss of the 2 protons). The 2-proton–2-neutron packet is, in fact, identical with the helium nucleus. These fast-moving helium nuclei are known as *alpha* rays, the term again first having been applied to the *alpha* rays of radium.

4. In consequence of the emission of the various particulate radiations, further energy adjustments may be necessary in the atom in order to achieve a balance and these may be served by the emission of radiation of an entirely different nature, not particulate, but consisting of electro-magnetic vibrations identical in nature with x-rays. These are the *gamma* rays, and the *gamma* rays emitted vary greatly in their energy, the least energetic being roughly equivalent to deep-therapy x-rays, while the most energetic would correspond to x-rays produced at voltages of several million volts.

It is the rule rather than the exception for more than one type of radiation to be emitted by radio-active substances. Thus, radium emits *alpha*, *beta* and *gamma* radiations. Radio-iodine emits *beta* and *gamma* radiations, while radio-phosphorus emits only *beta* radiations.

The Half-life

It has been seen that radio-active elements gradually disintegrate or decay. The rate of decay is extremely various in the different elements but for any given element it is fixed and immutable.

The decay of a radio-active element occurs in accordance with a curve well known to mathematicians. If a gramme of any radio-active element decays to half a gramme in x years, it will decay to a quarter of a gramme in a further x years, to an eighth of a gramme in a further x years, to a sixteenth of a gramme in a further x years, and so on. In fact, the time taken for a given quantity of any radio-active element to fall to half that quantity will always be the same, however large or small the initial quantity, and will always be the same for the same element. The period taken for a given quantity of an element to fall by half is called the half-life.

Half-lives vary greatly from radio-active element to element. Indeed, the variation is literally from a second or less to millions of years. Thus, the half-life of thorium is 89,000 years, that of radium 1,590 years, that of P^{32} (the phosphorus isotope usually used clinically) 14·3 days, that of radio-active iodine (I^{131}) 8 days, while as an example of a very short half-life, Xenon 143 has a half-life of one second.

In practice, radio-active isotopes used in therapy by injection are chosen so that their half-lives are sufficiently long to serve their purpose while being sufficiently short for safety. Recently a case was reported by Abrahamson of Dublin in which a patient had died from carcinomatosis of the lungs who had been given thorotrast injections some fifteen years previously. Radio-activity was detected in the liver of this patient after this long interval (short, however, in comparison with the half-life of thorium). The question has been raised as to whether this case should not point a caution in the use of radio-active isotopes. Although carcinogenic possibilities from radio-active isotopes cannot at present be ruled out, nevertheless, this particular case has little relevance to the risk, for only short half-life elements are used in isotope therapy.

The Atomic Pile—Atomic Fission

It has been seen that isotopes are produced by bombardment with nuclear particles, mostly with neutrons. Nearly all the isotopes in use in Great Britain are produced in the atomic pile, the principle of which is roughly as follows.

When one of the uranium isotopes is bombarded with neutrons under appropriate conditions, instead of the positive charge merely being clipped off the nucleus, so to speak, the nucleus can actually be made to break in two. This breakage is attended by an enormous outburst of energy. The energy outburst includes the setting free of large numbers of neutrons. The neutrons set free are in their turn available to add to the bombardment of any unsplit uranium and so the nuclear energy of a comparatively large mass of uranium can be set free practically instantaneously. This is, of course, the principle of the atomic bomb. Very fortunately, the chain-reaction by which the neutrons set free in the first nuclear fission set off further fissions tends to defeat itself and die out. It is clear, however, that if such a chain-reaction could be started by the fission of a small number of atoms and kept going in such a way that control could be exercised, a valuable source of energy would be available. This, is of course, the basis of hopes for the commercial utilization of atomic energy. In fact, this is possible and it is what happens in the atomic pile. A controlled chain-reaction is kept going indefinitely, and, in the course of it, very large quantities of neutrons are being produced. Accordingly, whenever it is required to submit any substance to neutron bombardment all that is necessary is that it is put in a suitable container and introduce it into the pile.

Detection and Measurement of Radiation—the Geiger Counter

The Geiger counter is an instrument which can detect a single *beta* particle, *alpha* particle or quantum (that is unit quantity) of *gamma* radiation. It usually consists of a short piece of tube with a central insulated electrode and it is filled with a suitable gas. A high voltage is connected between the wire and the case and this voltage is adjusted so that it is just insufficient to overcome the resistance of the gas. Accordingly, no current can flow between the

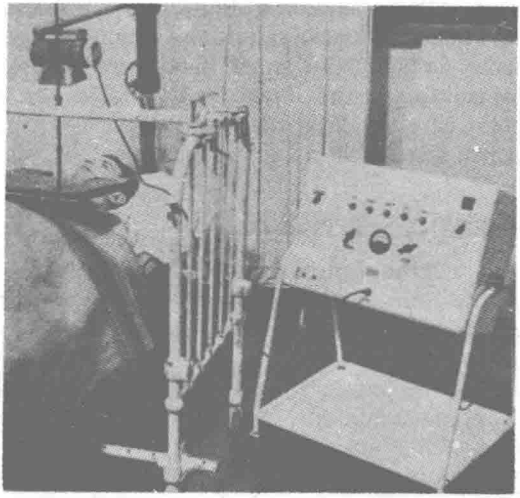


Fig. 2. A Geiger counter for clinical use.

central wire and the case. When a *beta* particle enters the chamber, it produces electrical disturbances known as ionization in the gas as a result of which, the resistance of the latter is momentarily lowered and the current momentarily flows. This current can be amplified and made to produce a click in a loudspeaker and the click will occur every time an *alpha* or *beta* particle or a *gamma* quantum enters the chamber. The demonstration of the clicking Geiger counter is quite impressive to anyone who has not seen it before. When brought into the vicinity of even a very weak radium source, the odd click, which is all that is ordinarily heard, and is due to cosmic radiation, becomes accelerated, and as the chamber is brought nearer and nearer to the source the clicks become more and more accelerated until eventually they become a continuous noise.

In the more elaborate instruments the counters are often connected to meters which read the number of counts per second and can be made to actuate light signals.

The unit of dosage of radiation is the r which will be explained later.

Radio-isotopes in Medicine

Radio-isotopes have at present two main uses in medicine : (1) the use of "labelled" elements in metabolic, circulatory and other studies, and (2) therapeutic use.

A "labelled" element is an element which contains a proportion of radio-active isotope so that when introduced into the body it can be traced by detection of its radio-activity. For example, a radio-active isotope of iron (half-life 44 days) is used in making studies of iron metabolism, and studies of the movement of sodium in the body have been made by means of radio-active sodium.

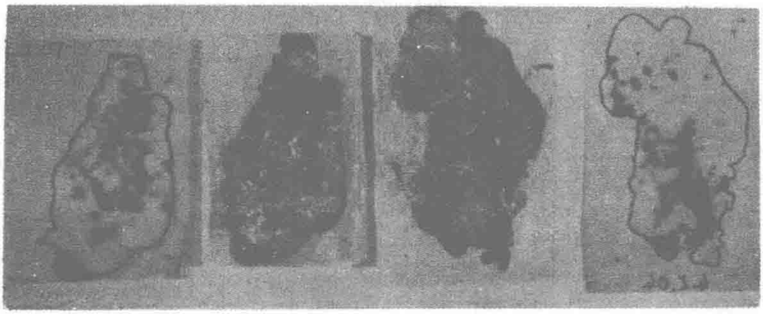
In the therapeutic field, the two best known isotopes at the present time are radio-active phosphorus and radio-active iodine. The radio-active isotope of phosphorus which is used is P^{32}. Normal phosphorus consists of atoms of 15 protons and 16 neutrons to the nucleus. That is to say, the atomic number is 15 and the mass number is 31. When an extra neutron is forced into the nucleus it becomes P^{32}. P^{32} is radio-active and emits *beta* particles whereby the extra neutron is changed into a proton producing the element of atomic number 16, which is sulphur. P^{32} has a half-life of 14·3 days. It must be remembered, however, that in the human body the disappearance of the radio-active isotope is hastened by excretion, so that the biological half-life, as it is called, is shorter than the physical half-life. Radio-phosphorus has achieved its greatest success in the treatment of polycythaemia. It has proved somewhat disappointing in the treatment of leukaemia and other conditions.

The radio-iodine isotope used in clinical work is I^{131}. Normal iodine has 53 protons and 74 neutrons, that is its atomic number is 53 and its mass number is 127. Iodine 131 has 4 extra neutrons. It emits *beta* and *gamma* radiation and its half-life is 6 days.

Radio-iodine can be detected by a Geiger counter over the thyroid gland within a few minutes of the administration of the labelled element. The uptake in hyperthyroidism is much higher than in the normal gland. The uptake in non-toxic goitre is somewhat greater than in the normal gland. The uptake of the thyroid in hypothyroidism is very low. Radio-active iodine is therefore important as a means of diagnosis in thyroid disease.

The therapeutic value of radio-active iodine lies in the fact that the concentration of the radio-active isotope in the organ results in the actual submission of the thyroid cells to intracellular radiation from the isotope of a much higher intensity than in other organs and tissues which absorb relatively little. Thus, thyroid activity can be depressed and even myxoedema can be produced.

Some carcinomas of the thyroid take up iodine selectively and so do some metastases from thyroid carcinoma. Remarkable results are occasionally obtained in the treatment of metastases from thyroid carcinoma by radio-active iodine.



Right Lobe *Left Lobe*

Fig. 3. Auto-radiographs of thyroid gland in Hashimoto's disease. The left-hand pictures are the auto-radiographs, while the right-hand figures are photographs of the cut sections of the gland. The blackened areas in the auto-radiographs show where normal thyroid tissue persists.

Radio-autography

Tissues which have taken up radio-active material can be made to demonstrate the distribution of the material photographically. A slice of the tissue is laid on a light-wrapped photographic plate so that the cut surface of the tissue is in contact with the surface of the protective wrapper. After an appropriate exposure the histological pattern of the cells which have taken up the radio-active material is found to be photographed on the plate. This is the process known as radio-autography or auto-radiography.