Introduction to Radiobiology

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Preface

The present book is both a translation and an update of the French book 'Radiobiologie' published in 1986. Many new developments have occurred during the intervening four years and the three authors and the translator have taken the opportunity to modernize the text and to include newer references. The structure of the book, however, remains the same.

The subject matter is primarily human radiobiology. The main emphasis of the book is the biological, physical and chemical basis of radiotherapy. An important section is concerned with the biological basis of radiation protection and the action to be taken in the event of a radiation accident.

Despite new developments in the treatment of cancer by surgery and chemotherapy, radiotherapy has not lost its importance and is used at some stage in about half of all cases. The new methods, such as the use of new drugs and immunotherapy, have not replaced the use of radiation; rather, they are combined with radiation to provide a more comprehensive means of attack.

Molecular biology has brought new insights towards understanding the principal mechanisms underlying cell death and loss of reproductive integrity following irradiation. In this respect the importance of repair of radiation-induced damage such as lesions has become increasingly evident.

Radiation protection is a subject of increasing importance. There is greater understanding of the damaging effects of irradiation than of the effects of any other noxious influence in the environment. Consequently the regulations controlling exposure to radiation have served as a model for other noxious agents. Medical use of radiation, mainly in diagnostic radiology, represents the principal contribution to the irradiation of the human population from artificial sources and is comparable in magnitude to that from natural background radiation. Nuclear methods of generating electricity have assumed an increasing share of the total during the last few decades but have added very little to the radiation received by the general population. Atmospheric pollution and fear of increasing global temperatures due to the burning of fossil fuels, together with lack of discernible progress towards the economic use of nuclear fusion, are arguments supporting the further development of reactors based on fission. At present this is held back mainly by fears of accidents such as that at Chernobyl. The gross disproportion between the anxiety felt by the population of Western Europe after Chernobyl and the reality of the hazard demonstrates the need for improved education of the public and of bodies responsible for public health and protection of the environment. The same was true, to perhaps a greater extent, for the population of the USA after the accident at Three Mile Island.

The aim of this book is to provide information to those concerned with the relevant fields of knowledge. We hope it will be of value particularly to trainees in radiology, radiation oncology and nuclear medicine and to scientists concerned with cancer or radiation. We hope it will also be valuable in general medical education and in the wider sphere of public administration in relation to the advantages and disadvantages of ionizing radiation in all areas of human activity.

We would like to record our thanks to all those who have given us advice on the content of this book. The list would be too long but we wish to thank especially G. Adams, M. Bertin, D. Chassagne, Ch. Chevalier, S. Field, J. Guelette, G. Hahn, H. Jammet, L. Lallemand, F. Laval, A. Léonard, E. Malaise, A. Michalowski, J. Ninane, N. Parmentier, P. Pellerin, and F. Zampetti-Bosseler.

Contents

Chapter 1.
Initial physical effects of irradiation: dosimetry – microdosimetry

The biological effects of irradiation are the end product of a long series of phenomena which are set in motion by the passage of radiation through the medium. The initial events are ionizations and excitations of atoms and molecules of the medium along the tracks of the ionizing particles. These physical perturbations lead to physico-chemical reactions, then chemical reactions and finally the biological effect. The sequence of these stages is represented schematically in Table 1.1.

Here we recall briefly the changes of energy in ionizations and excitations, the mechanisms which are at their origin and the dosimetric expressions which characterize their spatial distribution.

1.1 Slowing down of charged particles

Ionization – excitation

In matter the electrons have regular places in the structure of atoms, molecules or ions. To detach an electron, i.e. to produce ionization, it is necessary to supply a quantity of energy (symbolized by W) which represents its binding energy. Some examples of binding energies in atoms are given in Table 1.2. In the ground state the electron occupies the available places in the most strongly bound positions. The binding energy of the outermost electron which corresponds to the first ionization potential is of the order of 10 eV ($W = 13 \cdot 6$ eV for the atom hydrogen).

An electron can be carried into a more external orbit, normally empty, which constitutes an *atomic excitation*, e.g. in an atom of hydrogen the electron can be carried from the K shell into the L shell by giving it an energy of $10 \cdot 2$ eV. In molecules the energy needed to extract one of the outermost electrons (first molecular ionization potential) is of the order of 10 eV as for atoms. Rather lower energies may be able to produce excited molecular states.

It must be emphasized that the ionization energy is considerably greater than the energy of intramolecular binding, i.e. the chemical energy, which is, for example, $4 \cdot 9$ eV for the bond C=C and $5 \cdot 16$ eV for the bond H–OH. The ionized

Table 1.1. Chronology of events.

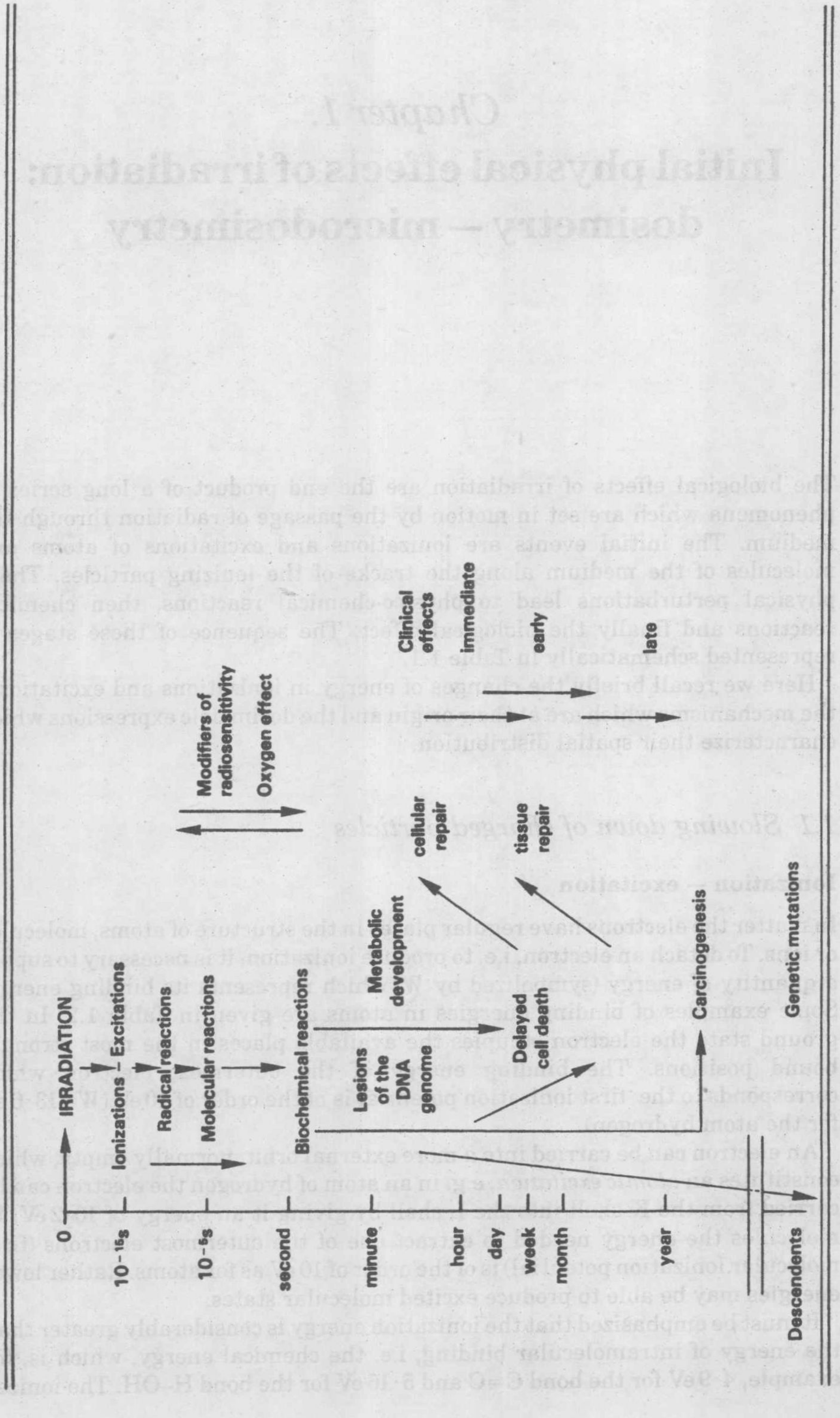

Table 1.2. Binding energy of electrons (eV).

Atoms					
		Shell†			
Atom	Z	K	L	M	N
H	1	13·6‡	(3·4)	(1·5)	
C	6	284	11·2		
O	8	532	13·6		
P	15	2142	128	10·9	
Ca	20	4038	346	47	6·1

Molecules	
H_2	15·6
O_2	12·5
H_2O	12·6
NO_2	11·0
CO_2	14·4

† For the L, M, N . . . shells only the lowest binding energy is given.
‡ The underlined figures represent the binding energies of the most weakly bound electrons (the first ionization potential).

molecule has an excess of internal energy equal to the energy of electronic binding supplied to provoke ionization, which is therefore more than enough to produce dissociation of the molecule. Molecular excitation can have the same consequence.

Ionizations and excitations are created in the medium when it is traversed by fast *charged particles* as a result of interactions with the electrons which are located close to their tracks. The radiation incident on the medium is classified as *directly ionizing* if it is composed of charged particles, e.g. electrons, protons, deuterons, heavy ions, etc. The radiations which are composed of uncharged corpuscles, photons and neutrons, produce ionization through the charged particles which they set in motion in the medium—secondary electrons in the case of photons and secondary protons in the case of neutrons (see later in this chapter); they are called *indirectly ionizing* radiations.

General mechanism of the interaction between moving charged particles and the electrons of the medium

The interactions between a charged particle and the electrons of the medium which it is traversing are the essential cause of the slowing down of the particles.† In addition, they are the origin of the absorption of energy by the medium and of the effects which result. The mechanism of interaction is common to all the charged particles and is shown in Figure 1.1.

The Coulomb force (of attraction or repulsion) which exists between the two electric charges during the brief passage of the particle close to the electron,

†Another cause of slowing down of charged particles is interaction with nuclei which results in the appearance of *bremsstrahlung*; this mechanism has a very important application, namely the production of X-rays by fast electrons bombarding a target of high *Z*. In biological media the slowing down of electrons or other charged particles by nuclear interactions is of very minor importance.

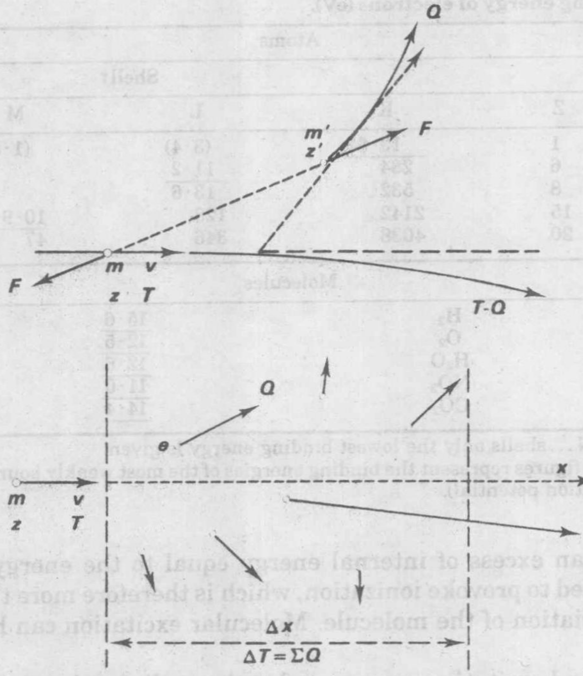

Figure1.1. Collisions of charged particles with the electrons of the medium. The Coulomb force acting between the incident particle (an electron in the case illustrated) and an electron of the medium involves the transfer to the latter of energy Q which is drawn from the energy T of the incident particle. Over a distance Δx the particle loses energy ΔT (the sum of transfers Q resulting from collisions occurring over this distance). The stopping power is defined by $S=\Delta T/\Delta x$; it depends (as does Q) on the speed and charge of the incident particle and on the number of electrons per unit volume of the medium.

gives an impulse to the electron; as a result there is a transfer to the electron of an energy Q which is derived from the kinetic energy T of the incident particle. The transfer of energy has a maximum value, Q_{max}, in the case of a head-on collision, the electron being exactly on the track of the incident particle.

Q_{max} depends on the mass of the particle:

(i) if this is an electron $Q_{max}=T$ (because the two electrons cannot be distinguished, it is convenient to consider the secondary electron as the one with the lower energy, which implies that $Q_{max}=T/2$);

(ii) for a particle of mass M very much greater than the mass m of the electron, $Q_{max}=4Tm/M$: for example, a proton cannot transfer to an electron more than 0·2% of its kinetic energy.

For distant collisions the transfer Q depends on the distance h between the electron and the trajectory of the particles, on the speed v and on the charge z of the latter:

$$Q=K\frac{1}{h^2}\,\frac{z^2}{v^2}$$

The transfer Q diminishes quickly as h increases; for example, a fast electron of 1 MeV transfers to an electron of the medium $Q=1$ keV for $h=10^{-6}\mu$m and $Q=10$ eV for $h=10^{-5}\ \mu$m. (One should note in this example what is represented by the distance h for collisions called 'distant' with small transfer of energy.)

For a given distance h, the transfer Q becomes greater as the speed of the particle becomes less because the impulse communicated increases with the duration of the interaction; for example, Q is 10 times greater for an electron of 10 keV ($v=6\cdot 10^9$m s$^{-1}=0\cdot 2\,c$, where c is the speed of light) than it is for an electron of 1 MeV (velocity approximately equal to c). A proton of 20 MeV has the same speed as an electron of 10 keV and produces the same transfer of energy Q. The transfer increases with the charge z of the particle proportionally to z^2; for example, for an α-particle ($z=2$) of 80 MeV, Q is four times greater than for a proton having the same velocity, i.e. an energy of 20 MeV.

Slowing down of charged particles — stopping power — trajectory and range

When a particle traverses a small segment Δx of its trajectory it suffers numerous collisions with electrons located at various distances from the track, corresponding to various transfers Q. The sum of all these transfers Q represents the energy ΔT lost by the particle over the distance Δx.

The ratio $S=\Delta T/\Delta X$ defines the *stopping power* (by collision) of the particle in the medium. S depends on the speed v and the charge z of the particle. If one considers as a first approximation that for each of these collisions the transfer Q is proportional to z^2/v^2, ΔT and hence S are equally proportional to z^2/v^2. A more exact formula established by Bethe takes account of 'close collisions' and of the role played by the binding of the electron to the atom.

At a given speed — the corresponding kinetic energy being proportional to the mass — all particles carrying a single charge (electron, proton, deuteron, meson) have the same stopping power. For protons of energy Tp, the stopping power is the same as that of electrons of energy Te$=T$p/1830 and of deuterons of energy Td$=2T$p; for an α-particle ($z=2$) of the same velocity and of energy $T\alpha=4T$p, it is four times greater. We will see (Chapter 11) that these differences in stopping power which depend on the speed and nature of the particles have radiobiological consequences.

A particle of initial energy T_0 traversing a medium progressively loses its energy over a distance R which represents its *range* (Table 1.3). For a heavy

Table 1.3. Heavy charged particles. Relation between the range (R) in water and the initial kinetic energy (T_0).

Particle			Range R (cm)		
Name	Symbol	Mass	5	10	15
			Kinetic energy T_0 (MeV)		
Proton	H^+	1	79	117	145
Deuteron	$^2H^+$	2	108	159	199
Helium ion (α-particle)	He^{2+}	4	297	464	584
Carbon ion	C^{6+}	12	1752	2620	3332
Neon ion	Ne^{10+}	20	3420	5918	7575

particle deviations caused by collisions are very small; the track is straight and its length does not vary between one particle and another. For an electron, distant collisions cause only very small deviations, but the rare close collisions involve large deviations: the track is composed of straight segments with sharp changes of direction; the end of the track is very convoluted. Close collisions involve large losses of energy which vary from one electron to another and the length of the track shows important fluctuations.

Effects of collisions on the medium

For the medium the effects of a collision depend on the energy Q transferred to the electron.

1. If Q is a little lower than the binding energy W (i.e. about 10 eV), the electron is not detached from the atomic or molecular structure to which it belongs. It can be taken to a higher energy level (*excitation*). Transfers of energy which are even lower are finally communicated to the molecule to increase its energy of translation, rotation or vibration, representing thermal forms of energy.
2. If Q is greater than W an *ionization* takes place. The electron carries off a kinetic energy $Q-W$ which is subsequently transferred to the medium to produce further ionizations, excitations and thermal transfers.‡ If Q does not exceed a few hundred electronvolts, the kinetic energy of the electron is absorbed in the immediate vicinity of its point of origin and a cluster of ionizations (and excitations) is produced. If Q is greater, the electron has a track distinct from that of the primary particle. It is then called a *δ-ray; δ*-rays are defined as secondary electrons set in motion by incident charged particles (which may themselves be electrons) whose kinetic energy is greater than a conventional value generally taken as 100 eV.

We have seen above that the transfer Q depends on the distance h of the electron from the track of the incident particle. As the electrons are dispersed at random in the medium, distant electrons are more numerous than those which are close and collisions with small transfers Q are more numerous than collisions with large transfers.

On the assumption that the electrons are free, it can be shown that the probability of a transfer Q is proportional to $1/Q^2$, e.g. the incident particle loses twice as much energy in collisions with Q between 50 and 51 eV as in collisions with Q between 100 and 101 eV. When the energy given to the electron is very small, its binding energy to the atom or molecule cannot be neglected; the momentum is then transmitted to the whole structure and on account of its large mass the transfer of energy Q is to all intents and purposes, zero.§

The distribution of energy lost by the particle as a function of the transfer Q is

‡A moving electron is called a sub-excitation electron when its kinetic energy is reduced to a level below the first excitation potential (6·6 eV for water) and it is called thermal when its energy is reduced to about 0·02 eV; the time required for thermalization is less than 10^{-12}s.

§The collision gives to the target particle an impulse or momentum $p=mv$ where m is the mass of the target particle and v the speed which is given to it. The corresponding kinetic energy is $mv^2/2=p^2/2m$; this is small if m is large.

shown schematically in Figure 1.2. It shows that the energy $\epsilon = \Delta t$ lost by the particle traversing a small segment Δx of its track is divided more or less as follows:

(i) 40% in transfers $Q > 100$ eV (δ-electrons);
(ii) 30% in transfers $100 > Q > 10$ eV (ionizations);
(iii) 30% in transfers $Q < 10$ eV (excitations and thermal transfers).

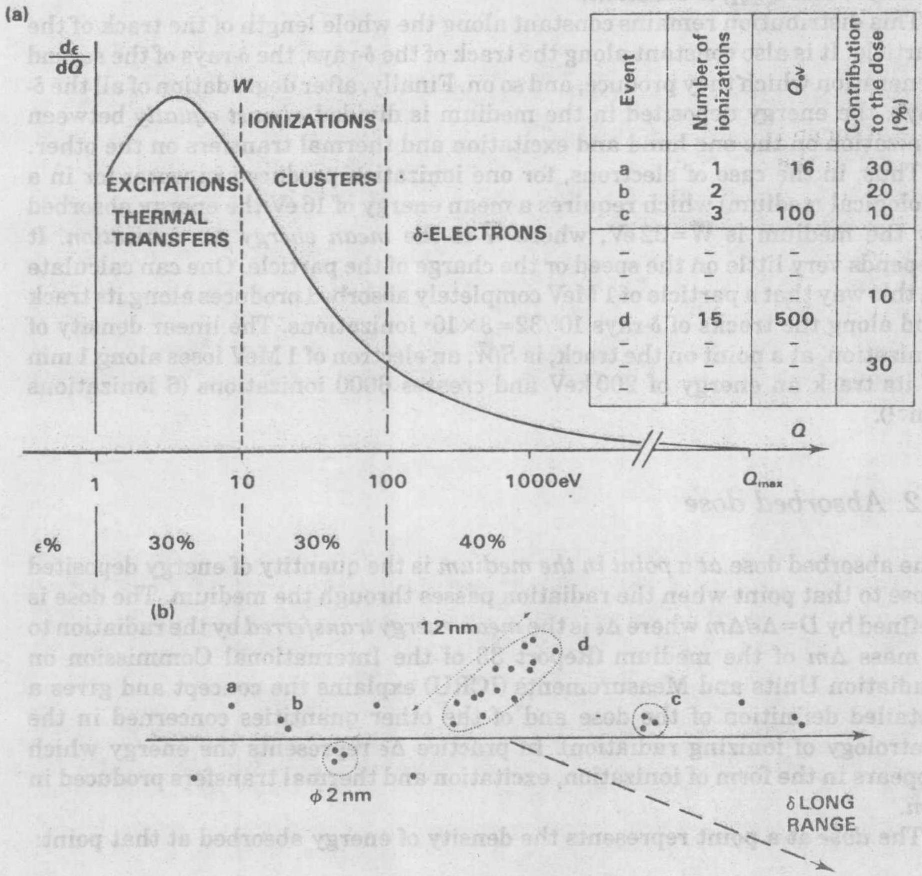

Figure 1.2. Distribution of energy lost by an incident particle as a function of the size of individual energy transfers.
(a) Along a small segment of its track, a particle loses an energy ϵ, the sum of individual transfers Q produced by its collisions (Figure 1.1). $d\epsilon(Q)$ represents the energy lost in transfers between Q and $Q+dQ$. The distribution is represented schematically in the figure (actually there are some variations depending on the nature and energy of the particle and on the medium). Depending on its size, a transfer Q above the binding energy W (taken here as equal to 10 eV) results in an ionization, a group of ionizations or a δ-electron (if $Q > 100$ eV); a transfer Q a little below W causes an excitation.
(b) Depending on the size of the transfer Q resulting from a collision, 1, 2 ... $n = Q/\bar{W}$ ionizations are produced in the medium. The different types of event are shown in the figure as well as their relative contributions to the production of ionizations, i.e. to the dose. The diagram does not indicate the proportion of different types of event (a is three times more frequent than b and 10 times more frequent than c, etc.). The mean separation of events depends on the LET: when the LET is 25 keV μm^{-1} (1 MeV protons) the groups of diameter 2 nm are contiguous.

This distribution is essentially linked to the relative frequency of close and distant collisions, which is fixed by the random spatial distribution of electrons in the medium. It depends to only a small extent on the speed of the particle or on its charge and so on its stopping power. We have seen above that the transfers Q are individually proportional to the stopping power but their relative frequency, if one takes into account distant collisions with Q very much smaller than Q_{max}, is constant.

This distribution remains constant along the whole length of the track of the particle. It is also constant along the track of the δ-rays, the δ-rays of the second generation which they produce, and so on. Finally, after degradation of all the δ-rays, the energy deposited in the medium is divided *almost equally* between ionization on the one hand and excitation and thermal transfers on the other.

Thus, in the case of electrons, for one ionization produced in water (or in a biological medium) which requires a mean energy of 16 eV the energy absorbed by the medium is $\overline{W}=32$ eV, where $\overline{W}$ is the *mean energy per ionization*. It depends very little on the speed or the charge of the particle. One can calculate in this way that a particle of 1 MeV completely absorbed produces along its track and along the tracks of δ-rays $10^6/32=3\times10^4$ ionizations. The linear density of ionization, at a point on the track, is $S/\overline{W}$; an electron of 1 MeV loses along 1 mm of its track an energy of 200 keV and creates 6000 ionizations (6 ionizations μm^{-1}).

1.2 Absorbed dose

The absorbed dose *at a point in the medium* is the quantity of energy deposited close to that point when the radiation passes through the medium. The dose is defined by $D=\Delta\epsilon/\Delta m$ where $\Delta\epsilon$ is the *mean energy transferred* by the radiation to a mass Δm of the medium (Report 33 of the International Commission on Radiation Units and Measurements (ICRU) explains the concept and gives a detailed definition of the dose and of the other quantities concerned in the metrology of ionizing radiation). In practice $\Delta\epsilon$ represents the energy which appears in the form of ionization, excitation and thermal transfers produced in Δm.

The *dose* at a point represents the density of energy absorbed at that point:

$$D=\Delta\epsilon/\Delta m$$

Because of the discontinuous nature of the events which lead to the absorption of energy, dose is meaningful only when the mass Δm is great enough that there is neither an appreciable statistical fluctuation in the number of particles traversing such a mass during the irradiation nor in the energy which they deposit.

The unit of dose is the gray (Gy): $1\,Gy=1\,J\,kg^{-1}$. (An old unit, the rad, is $10^{-2}\,Gy=1\,cGy$.) The dose also represents the density $\Delta n/\Delta m$ of ionizations produced at the point considered.

$$\Delta n/\Delta m=(\Delta\epsilon/\overline{W})\times 1/\Delta m$$

In water ($\overline{W}$=32 eV) a dose of 1 Gy (=$0{\cdot}6\times10^{19}$ eV kg^{-1}) corresponds to a density of ionizations equal to 2×10^{17} ionizations kg^{-1}, i.e. 2×10^{5} ionizations for a cell of mass 10^{-9} g.

The measurement of dose is not considered here. We recall only that the normal method is to use an ionization chamber: the principle is to measure the density of ionization in a small volume of air placed at the point considered and to deduce the density of ionization or the energy absorbed in the dense medium.

The dose is a quantitative expression of the physical effect produced by the radiation at a point in the irradiated medium. It has biological interest because the biological effect is related to it. The distribution of dose in a region of the body exposed to a particular radiation gives a representation of the biological effect produced at each point and for equal doses the biological effect is the same for a given radiation. However, the relation between the biological effect and the dose depends on the nature of the radiation; the quantitative character attached to the notion of dose must be complemented by its qualitative character which is studied in Section 1.4.

1.3 Dose distributions from beams of radiation

We limit ourselves in this work to the general characteristics of the variation with depth of the dose delivered by beams of radiation currently in use in radiobiology and radiotherapy. We also consider the characteristics (nature and energy) of the ionizing particles set in motion in the irradiated medium and their variation with depth; these characteristics are of radiobiological importance because they govern the distribution on a microscopic scale of the absorbed energy (Section 1.4) and the biological effectiveness of the radiation (Chapter 11).

Beams of heavy charged particles

The heavy charged particles are atomic nuclei. We have seen above that their tracks are straight and that they have a definite range depending on their nature and on their kinetic energy (Table 1.3).

The velocity of these particles diminishes steadily with depth resulting in an increase in the stopping power and at the same time an increase in dose. All beams of monoenergetic heavy charged particles produce a characteristic form of dose distribution (Bragg curve) with a sharp peak close to the end of the range (Figure 1.3). As the Bragg peak is very narrow the dose distribution produced by monoenergetic particles is not usually suitable for radiotherapy. To deliver a uniform dose over a greater thickness, the energy of the particles must be modulated during the irradiation in order to shift the peak; in this way the peak is widened at the cost of a reduction in its height.

Heavy charged particles for external beam radiotherapy are produced by powerful accelerators (cyclotrons or synchrotrons) which provide the large kinetic energy required to attain the necessary depth (Table 1.3). For protons the range exceeds 5 cm when the energy is above 80 MeV. At these energies the stopping power (or the linear density of ionizations) is low at the entry surface of the medium. It increases slowly at first in the course of slowing down of the