elucidation on the subject of carcinogenesis is offered in the study 'Radiation carcinogenesis in experimental animals' by J. J. Broerse, D. W. van Bekkum and C. Zurcher. The field of radiation damage on animals is rounded off by C. Michel with the contribution 'Radiation embryology'. Damage to proliferating organisms is one of the most impressive effects of radiation.

I very much thank my friends and colleagues for having written such remarkable and excellent contributions to clarify the complex effects of radiation on living matter.

Hedi Fritz-Niggli

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Radiation physics

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Summary. A review is presented of the recent literature in the areas of physics which deal with radiation effects on man and animals. Some consideration is given to natural and artificial radiation sources such as cosmic rays, radon and high energy accelerators. The interaction of radiation with matter is treated if it is related to an energy deposition pattern relevant to biological effects. Dosimetry is also treated, with special emphasis on papers dealing with spatial dose distribution on a microscopic level, and radiobiological models relating the energy deposition pattern to biological effects are cited. New techniques in the medical application of radiation in diagnostics and therapy are briefly mentioned.
Key words. Radiation sources; energy deposition; charged particles; dose; models; medical applications.

Of the many types of radiation, which – even if only electromagnetic waves are considered – range from radiowaves over microwaves, heat, visible and ultraviolet light to X-rays and gamma-rays, this article is concerned only with ionizing radiations.

Radiation sources

Natural radiation sources

Since the big bang, the universe has been filled with radiation, and the earth is bombarded continuously by particles and photons from space with different frequencies and different origins [1, 24, 82–84]. The most abundant particle is the proton, but, nuclei up to the mass of iron are also present in the cosmic radiation, although with lower frequencies. For manned space flight these may be as important as protons because of their higher ionization densities [54]. Depending on the type and energy of the radiation, the magnetic field of the earth and the atmosphere act as a shield, eliminating some of the particles completely and reducing the intensity of others. The earth is therefore protected from the large showers of particles which traverse space. The mathematical description of these radiation fields is the aim of some of the recent papers [82, 83]. For our planet an important source of radiation is the sun where, as a result of the fusion process, neutrons, photons and charged particles are emitted, the intensity showing a correlation with the solar activity. On earth, cosmic radiation accounts for approximately 10% of the natural radiation dose.

A larger contribution to the natural radiation burden of mankind is made by irradiation by daughter products of the decay of radon, present in changing concentrations in the crust of the earth. Radon gas diffuses from the rocks in the ground to the surface; owing to variations in radon occurrence and in diffusion conditions, considerable geographical differences are registered. But for man, the dose is even more dependent on the habits of individuals; the exposure outside is smaller compared to that inside buildings, and even inside, substantial differences exist. The radon problem was the subject of a special issue of the journal 'Health Physics' in 1983 with a number of review articles [29, 63, 65]. Special attention has been given to the rate of air exchange, more specifically, the correlation of radon exposure with the construction of energy-conserving houses [14, 64]. Other important parameters are the height above ground and the construction materials, which both influence the exposure to radon daughters [42]. Other sources of radiation which contribute substantial doses, but to limited groups of people, are the monazite sands in Kerala, India [28], and in Guarrapari, Brasilia [4]. Apart from external radiation sources all creatures are also irradiated by internal sources, with a comparable dose. The exposure is the result of isotopes incorporated in our body such as ^{40}K, ^{14}C, ^{210}Po and some other elements which emit electrons, alpha-particles or gamma-rays [78]. The dose due to internal irradiation is not uniformly distributed throughout the body, owing to selective incorporation by some tissues.

Artificial radiation sources

Since the discovery of X-rays by Conrad-Wilhelm Röntgen in December 1895, generators of ionizing radiation have been sources of both intentional and accidental exposure of man to radiation. Since then many new machines have been built, accelerating charged particles to much higher energies and producing beams of higher penetration or beams of higher intensity. Many of these accelerators have been built for physics research but most of them have also stimulated research in radiation biophysics, leading to radiobiological and medical innovations. The first goal of radiobiological research has usually been the study of the interaction of new forms of radiation with biological materials and the determination of radiobiological effectiveness in various biological test systems. Many of the physics research facilities have developed a tradition of radiobiological research. A major stimulus for this work was usually the determination of the potential radiation hazard to experimenters and accelerator personnel from new radiations; however, some work was done in the expectation of finding hitherto unknown biological reaction mechanisms due to new energy deposition patterns. Many of these beams had very low intensities and it was difficult to conceive applications other than radiation protection experiments (as, for example, radiation treatment). But some of the new facilities did develop high current accelerators with intense charged particle or neutron beams, which could be used for radiotherapy [69].

A new generation of physics accelerators will again provide a novel radiation source for biology and medicine. Accelerators have been built, and others are planned, which are powerful sources of synchrotron radiation [51]. Besides UV-light these accelerators provide soft X-ray sources with intensities which are several orders of magnitude higher than those produced by conventional X-ray generators, allowing experiments with heavily filtered or even scattered, monoenergetic beams; radiobiological experiments as well as diagnostic applications will be possible [13].

The most important artificial radiation sources are nuclear reactors. In many countries at the present time they are under increasing political pressure. The problem is not the normal operation of the power stations, during which the radiation emitted is small, but the risk of a meltdown on the one hand, and the radioactive wastes produced on the other hand. After a number of near-accidents, and particularly after Chernobyl, the safety of nuclear power stations is being seriously questioned [52, 55, 76].

Reactors as well as accelerators are used to produce radioactive isotopes which are an important diagnostic tool in analyses of chemical, biological or other pathways, but which can also be used in some cases in radiotherapy.

Interaction of radiation with matter

Particles

In physics research more and more elementary particles have been detected. The newly discovered particles such as quarks are essential parts of a new unified description of forces and elementary particles. For the treatment of radiation effects on man and animals, however, these new particles are not relevant. For our purpose all particles can be divided into a few groups, depending on charge and mass.

For practical purposes, the most important particle for the interaction of ionizing radiation with matter is without doubt the *electron*. Even if the primary particle is an energetic heavier charged particle or a photon the greater part of the energy transferred to the target material is transferred by secondary electrons of various energies. Even though the mechanisms of the reaction of electrons with matter have been known for a long time [25, 56], new treatments of this field have been published. Electrons interact with matter by collisions with electrons of the atomic shell or with the charged nucleus. As a result of the long range of the coulomb force acting between charged particles, the interactions are very frequent and they can be treated with statistical methods. The type of interaction as well as the frequency is strongly energy-dependent. For high energy electrons the interaction results in low local concentrations of ionizations and excitations of target molecules, whereas at the end of the track the concentration increases. Secondary electrons cannot be distinguished from primary electrons; they experience the same interactions – elastic and inelastic scattering, or the production of Bremsstrahlung. Computer programs have been written to calculate energy loss and range or to simulate electron tracks in biologically relevant media [5, 44, 66].

The interactions of *heavier charged particles*, like mesons, nucleons and heavy ions, have also been the subject of further investigations. Protons, pi-mesons and heavy ions especially have already been used for radiation therapy, owing to the fact that they experience a smaller scattering as a result of their larger mass. The negative pion, the lightest of these particles, owes its role in radiotherapy to the fact that it can be captured by a target nucleus and thereby emit secondary charged particles as well as neutrons and photons. The multiple scattering and the range straggling are larger than for the other heavy particles [6, 7, 25, 69].

The tracks of all heavy charged particles are characterized by a large number of secondary electrons produced by interaction of the particle with the medium. The range and density of the secondaries are responsible for the efficacy of a particle in producing damage in biological systems; they are a function of the velocity and the effective charge of the projectile [25, 30, 43, 68, 73, 74, 80]. From the cross-section data for the interactions, track structures in biologically relevant media, like water or tissue equivalent (TE) gas, can be calculated as a basis for the analysis of biological data [33, 45, 48, 61]. Track structures of heavy, fast charged particles (HZE) are of special importance for space flight.

Neutrons, as uncharged particles, do not experience long-range electrical forces. A characteristic common to neutrons and other uncharged particles is that they interact with material in discrete interactions when there is a short distance between the interacting partners [58-60, 75].

Neutrons, depending on their energy, have various reaction channels [25, 56, 57]. Elastic and inelastic scattering with hydrogen or with heavier nuclei lead to moderation of the neutrons but also to the emission of charged and neutral secondary radiation. Neutron dosimetry, owing to its importance in radiation protection and in radiotherapy, has received considerable attention [3, 12, 15, 36, 37]. Of special interest in this respect is also the reassessment of the dosimetry from the Hiroshima and Nagasaki atomic bombs, resulting in a reduction of the neutron dose estimate for both cities [26, 71].

Interaction of electromagnetic waves with matter

Photons, i.e. gamma-rays if they originate from the nucleus, and X-rays from the atomic shell react by photoelectric effect, Compton scattering or pair production [10, 25, 56]. Very low energy X-rays which produce photo-electrons with nanometer ranges are used as a tool to study models of biophysical action [11, 70]. Each energy interval is dominated by a different interaction mechanism.

Measurements, units

Dose

To analyze the effect of radiation a quantitative description of the energy deposited in a volume element is necessary. To guarantee uniform results international recommendations exist for a number of specific situations [36-41]. Especially in radiotherapy, these are supplemented with additional national or international recommendations for specific radiations or situations. The units to be used are now the SI-units, i.e. the Gray which is 1 Joule/kg, instead of the rad which was used earlier; 1 Gy is equal to 100 rad [40]. Even though the dose is the most important single parameter to describe an exposure to ionizing radiation, the effect may be dependent on other parameters like energy distribution in time and in space, both on a microscopic and on a macroscopic scale. Very often the dose cannot be measured in situ in a human or in an animal; it is therefore measured in air or in a phantom and the data is used to calculate the dose at the point of interest. For this conversion the tissue composition, the phantom and detector composition as well as the details of the geometry of the measurement and of the exposure have to be taken into account. The knowledge of the energy spectra of the particles involved may be also of crucial importance.

Dose rate

The primary process of energy deposition in a medium is followed even in anorganic probes by dynamic processes like the recombination of ions; in living organisms these dynamic processes may extend to repair involving much longer time intervals. After the interaction of a first particle with the sample, reaction products may still be available for reactions with species produced by another particle, crossing the same volume. Recombination of radiation products is especially important when measuring radiation fields with high dose rates, or pulsed radiation, as the detection efficiency may be reduced substantially [41].

Spatial dose distribution

The radiobiological effect of radiation is not only dependent on dose but also on the spatial dose distribution within the relevant structure, for example the chromosome. It is well known that the average distance between ion pairs produced by charged particles is dependent on parameters like the charge of the projectile and its velocity, and that large variations occur in small volumes. To analyze such local energy deposition patterns microdosimetry is a possibility which has often proved to be useful [49, 50, 72]. Microdosimetric measurements are done with a gas-filled proportional chamber simulating a tissue volume between 0.5 and 2 µl. The event size spectra measured can be converted mathematically into linear energy spectra; often averaged values are used, like the frequency mean or the dose mean value, or a specially weighted value V^* which takes biological response into account. The information gained is not only of importance in radiation protection but it also helps to characterize high linear energy transfer (LET) fields for radiobiology or radiation therapy with neutrons, for example. Even though this measurement gives detailed information on energy deposition in microscopic volumes, the volume used is still much larger than for example the diameter of a DNA helix. Another technique to analyze energy deposition patterns is the simulation of particle tracks by Monte Carlo calculations. With the fast computers available today the path of particles can be followed if the interaction cross-sections are known. This has been done for electrons and for heavier particles [27, 31, 33, 44, 67].

Radiobiological models, if they are to predict radiation response in dependence on radiation quality, have to consider the energy deposition pattern. For this purpose none of the models uses an average value like mean LET. Some of the models allow for radiation quality differences in a general way, considering different pathways for low and high LET radiations [21, 22, 35, 53, 77, 79, 81] or for low dose or low dose rate [9, 21, 79]. Other models take the energy deposition pattern, based on microdosimetry or more often on Monte Carlo calculations, into account in more detail [8, 32, 33, 62].

Of special interest in respect to spatial dose distribution are Auger cascades [17-19, 46, 47, 67]. If a vacancy is created in some way or other in an inner shell of an atom, this hole can be filled by another electron of the same atom. By doing so the electron emits a photon which in turn can kick out an electron, still from the same atom, and the same process can be repeated several times. Even though there are only electrons and low energy photons involved, the energy density may be unusually high due to the fact that all these particles originate form the same atom. As the range of the electrons is short, it is crucial whether this cascade happens in a sensitive structure or outside [20].

Use of radiation in medicine

Medical use of radiation is responsible for the largest part of the artificial dose contribution to the radiation burden of man in the civilized world. A large number of invaluable technics have been developed, making use of radiation for diagnostics and therapy. Historically X-ray diagnostics was first, and it is still used very widely; many developments have improved equipment and imaging devices. Today more information can be gained with lower exposure of the patient. With the development of the digital technique new equipment has become available like the computer tomograph (CT) which allows three-dimensional reconstructions of internal structures of the body. More recently, with positron emission tomography (PET) a technique has become available where compounds loaded with specific isotopes emitting positrons can be followed in the body in real time, allowing studies of the metabolism in selected tissues with remarkable spatial resolution.

Even though more and more techniques have been developed which are not based on radiation, such as ultrasound and magnetic resonance imaging (MRI), radiography, CT, PET and other techniques using radiation do not seem to be threatened.

Shortly after their discovery X-rays were used for the first time in an attempt to cure patients of cancer. Photons of higher energies and correspondingly better penetration have been used for the external treatment of deep-seated tumors. Continuous improvement of the techniques has helped to improve the ratio of the dose to the tumor to the dose to the normal tissue, an important factor for complication-free cure. For specific situations electrons with a better-defined range are used routinely. Worldwide, a number of projects have been developed to improve therapeutic results by using other particles. For physics reasearch, accelerators have been built with a high proton current to produce very high intensity π- and μ-meson beams – so-called meson factories – to study rare events. At all three of these facilities in the West, LAMPF, Los Alamos (USA), TRIUMF, Vancouver (Canada), and SIN, Villigen (Switzerland), special beam lines have been dedicated to the use of negative pions in radiobiology and radiotherapy [6,23,69]. The proton accelerator at Harvard, Cambridge (USA), and the heavy ion accelerator at Berkeley (USA) are also used for patient treatment [2,16]. For radiotherapy with neutrons, hospital-based neutron generators have been built. Neutrons have been used where the radiobiological sensitivity of the tumor cells, e.g. as a result of anoxia, was expected to be the major problem. Protons are used where a precisely defined range would make it possible to protect an adjacent critical normal tissue, and finally heavy ions and pions where dose distributions and increased RBE for the tumor seemed to be important [69]. Still other techniques are under investigation, such as therapy with radionucleids and neutron-capture therapy; for the latter boron, which emits an alpha-particle after capture of a thermal neutron, is bound to a tumor-seeking molecule to achieve an exclusive irradiation of the target cells [27,34].

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Biochemical aspects of radiation biology

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Summary. In order to analyze the mechanisms of biological radiation effects, the events after radiation energy absorption in irradiated organisms have to be studied by physico-chemical and biochemical methods. The radiation effects in vitro on biomolecules, especially DNA, are described, as well as their alterations in irradiated cells. Whereas in vitro, in aqueous solution, predominantly OH radicals are effective and lead to damage in single moieties of the DNA, in vivo the direct absorption of radiation energy leads to 'locally multiply-damaged sites', which produce DNA double-strand breaks and locally denatured regions.
DNA damage will be repaired in irradiated cells. Error free repair leads to the original nucleotide sequence in the genome by excision or by recombination. "Error prone repair" (mutagenic repair), leads to mutation. However, the biochemistry of these processes, regulated by a number of genes, is poorly understood. In addition, more complex reactions, such as gene amplification and transposition of mobile gene elements, are responsible for mutation or malignant transformation.
Key words. Radiation effects; radiolysis; radicals; DNA damage; DNA strand breaks; nucleoprotein; base damage; DNA synthesis; DNA repair; mutagenic repair; error prone repair; gene amplification; transposition; endonuclease.

Introduction

To understand the mechanisms involved in the biological effects of ionizing radiation, the individual steps that take place after the absorption of radiation energy in living organisms have to be analyzed by biochemical methods. Such steps are the primary physico-chemical events affecting biomolecules, leading to molecular structural alterations, especially in the desoxyribonucleic acid (DNA). The study of radiolytic reactions in irradiated aqueous solutions of biomolecules results in a basic understanding of the events affecting these molecules in vivo, i.e. in irradiated organisms. One major difference between in vitro and in vivo observations is that in vivo, in addition to the action of radicals formed in water, the direct absorption of radiation energy is responsible for alterations of biomolecules leading to the biological radiation effect.

DNA damage will be reduced in irradiated organisms by subsequent repair reactions. Most of the repair reactions lead to full recovery of the cell, i.e. they are error free. Other repair reactions lead to an altered nucleotide sequence in the DNA, i.e. under certain circumstances to a mutation. Such reactions are described hereafter as error prone or mutagenic repair. At present the enzymatic processes involved in these DNA repair reactions are the main topic of biochemical studies in radiation biology. They may contribute to the mechanisms of the cellular and genetic endpoints of radiation effects as cell death, chromosome aberrations, mutations and carcinogenic transformation to a tumor cell.