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100 years of radiobiology: implications for biomedicine and future perspectives

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Abstract. The development of radiobiology from the very early detection of the biological action of X-rays to the knowledge of today is described in sections on radiation chemistry and biochemistry, mutation and cancer induction, and embryonic damage, as well as the dependence of radiation response on radiation quality and temporal dose distribution (repair) and the interaction with other factors. For medicine radiobiology serves as a basis for radiotherapy and radiological protection. The effect of very low doses, and their possible biopositive effect (hormesis and adaptive response), is also discussed, as are the health hazard of radon, health risks after the Chernobyl accident, and space radiobiology. The radiobiology of the future will be concerned with biomolecular and genetic implications, problems of damage and repair, and connected problems like hormesis.
Key words. Radiation chemistry; radiation biochemistry; cellular radiobiology; mutation induction; cancer induction; repair; space radiobiology; Chernobyl accident; hormesis.

History

The discovery of X-rays by W. C. Roentgen introduced the sciences of radiology: their biological aspects creating radiobiology and radio therapy, and their physical side creates X-ray diagnostics. Directly after their discovery (table 1) it was observed that X-rays can affect organic matter and living organisms. But these harmful effects could be exploited in a beneficial way in the destruction of cancer cells.

Early discoveries of the biomedical effect of X-rays

The news of the discovery of Roentgen was spread rapidly, reaching England and America by telegram. So it is not surprising that the first report of a biomedical effect originated from America, namely from Grubbé[35], who on 29 January 1896 had noticed he had a dermatitis apparently caused by X-rays. He later X-ray-treated (on the advice of his doctor) a chest-carcinoma and a Lupus vulgaris, but there is nothing known about the result. However, an analgesic effect after the X-ray treatment of a carcinoma was reported[28] in February. In July 1896[21] a clear regression of an irradiated gastric carcinoma was observed for the first time. Skin-reactions like erythema and epilation were reported early[19,25,26,56,60,80]. These biomedical changes were discovered almost exclusively as side-effects of irradiating persons in connection with early X-ray diagnostic experiments.

The experiments of Lortet and Genoud (June 1896)[57] are considered to be the beginning of a genuine experimental radiobiology. They injected tuberculosis bacteria into the inguinal area of 8 guinea pigs. The injection sites of 3 animals were irradiated daily for 8 weeks. While these animals remained healthy, the others fell seriously ill.

First phase of radiobiology: compilation of data and facts

After the pioneer experiments on cress and on mustard seedlings (causing inhibition of germination) as well as on rabbits and guinea pigs (causing damage to the male germ-cells; 1903[4]), a wide range of experiments was

Table 1. Early detections of the biomedical actions of X-rays.

	Implications to biomedicine	Author
January 29 1896	dermatitis, irradiation of a breast carcinoma and a lupus vulgaris	Grubbé[35]
February 3 1896	irradiation of a nasopharynx carcinoma, palliation effect	Voigt (vide Freund)[28]
March 1896	irritations of eyes	Edison[25]
March 1896	epilation	Thomson[80]
April 10 1896	epilation	Daniel[19]
May 8 1896	erythema, skin affections similar of sunburn	Science 3, p. 701
May 1896	erythema	Feilchenfeld[26]
July 9 1896	erythema	Leppin[56]
July 23 1896	dermatitis and alopecia	Marcuse[60]
July 1896	irradiation of a stomac carcinoma regression	Despeignes[21]

carried out. First hints of the effect on the genome came from fertilization experiments with unirradiated amphibian eggs and irradiated sperms in 1907 (ref. 7). Further experiments on amphibians, in 1911 (refs 41, 42), and on plants (thorn-apple and barley) followed. However the systematic experiments of Muller in 1927 (ref. 64) on the fruitfly Drosophila are regarded as a major step in this field. With the application of an ingenious method (CIB-technology) he showed clearly the quantitative and qualitative mutagenic effect of high energy radiation. With these experiments, which were later extended to mammals, the era of radiogenetics started.

The first radiobiological rule found was the growth delay[9] of proliferating tissues caused by irradiation. It was postulated in 1904 that the more a cell is capable of proliferation and division the more sensitive it is to irradiation. In fact this has not proved true for all cells, e.g. resting adult lymphocytes are very sensitive to irradiation. Interference with mitosis was described in *Vicia faba*, *Ascaris*, and *Pisum sativum*. A rhythm in the interference with mitosis was described in irradiated cancer tissue in 1922 (ref. 52) and was described comprehensively in 1923 and 1924 (refs 2, 3) with *Urodeles* larvae.

Disturbances of development are probably the most impressive somatic effect of irradiation. The effect of irradiation on amphibians and on sea urchin embryos was investigated early (1903)[11], and later Ascaris and chicken embryos. An experiment on a pregnant cat was carried out in 1905 (ref. 82), which was followed by investigations with guinea pigs and rabbits. An irradiation-induced human deformation was reported, presumably for the first time, in 1910 (ref. 29; further data 31). The induction of cancer by irradiation was discovered empirically in humans first of all. In 1911 (ref. 44) 54 cases of radiation cancer, which was called X-ray carcinoma, were presented. In 1910 (ref. 61) sarcomas were induced for the first time in irradiated rats. Later investigations on skin carcinomas in rabbits followed. Further data on the induction of pathological changes in mammal organs are given in ref. 30.

Second phase: development of hypotheses and theories

After the empirical and experimental phase of data collection, experiments looked for a relation between dose and effect. For both therapeutic and protective purposes the relationship between dose and effect is of fundamental importance. It was postulated early (1922)[10,22] that biological radiation effect curves are not sigmoidal, as with other damaging agents, but are closely related to the quantal discontinuous quality of energy-rich radiation. To show a reaction to radiation the object must receive hits with a dose-dependent probability. These hits represent absorption events, ionizations (according to the original idea of Dessauer, 'point warmth'). The hit theory was expanded to the target theory in which a volume (a target) was demanded in which the hits would cause an effect. In the proceedings of Lea (1946)[55] and Timoféff-Ressovsky and Zimmer (1947)[81] the hit theory had its culmination. Many theoretical analyses of the dose-effect curves followed later, in which e.g. microdosimetric considerations and dependencies of the effect on radiation quality and on recovery were included[51].

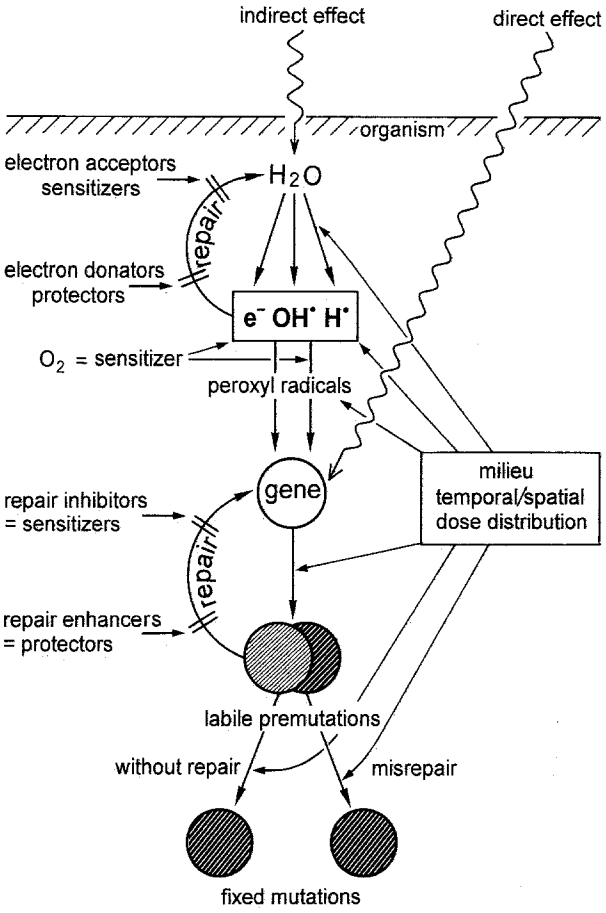

Figure 1. Radiobiological chain of events.

Some fundamentals of radiobiology today

The reaction chain of the biological radiation effect (see Birkenhake and Sauer in this issue) is complex and involves different fields of science. The path from the primary physical event (fig. 1) to the observable biological effect can be short, but it is usually long. Different intermediate stages are possible, which can be influenced by several factors and are partially reversible. Generally there are two possible modes of action of high energy radiation. In the direct effect, the physical primary event is practically identical with the biological effect. In contrast the indirect biological effect is induced by chemical radiation products.

Table 2

Primary reactions

1) $H_2O \xrightarrow{\text{radiation}} H_2O^{\cdot+} + e^-$ (Ionization)

2) $H_2O \xrightarrow{\text{radiation}} H_2O^*$ (Excitation)

1a) $H_2O^{\cdot+} + H_2O \rightarrow H_3O^+ + {}^{\cdot}OH$ (radical)

$e^- + nH_2O \rightarrow e^-_{aq}$ (solvated electron)

$e^-_{aq} + H^+ \rightarrow H^{\cdot}$ (radical)

2a) $H_2O^* \rightarrow H^{\cdot}$ (radical) $+ {}^{\cdot}OH$ (radical)

Further reactions

${}^{\cdot}OH + {}^{\cdot}OH \rightarrow H_2O_2$, $H^{\cdot} + H^{\cdot} \rightarrow H_2$, $H^{\cdot} + {}^{\cdot}OH \rightarrow H_2O$ in dependence of LET (radiation quality) and O_2 concentration

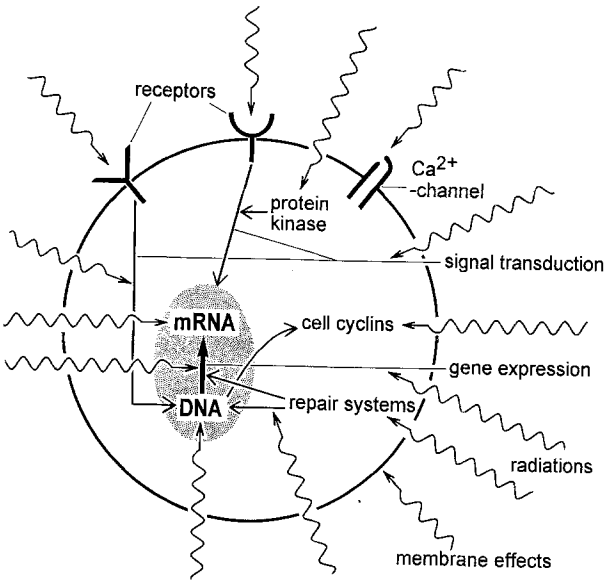

Figure 2. Possible cell alterations after irradiation. Ionizing radiation can influence the DNA and the gene expressivity directly and indirectly by disturbance of receptors and signal transduction, by production of protein kinase, by damaging the repair systems. Beside and (or) connected are membrane effects and influences on Ca^{2+} channels.

Radiochemistry of irradiated water

Biomolecules in aqueous solution are presumably the starting-point of many biomedical processes. The irradiation-induced change in water is therefore of great interest (table 2). The water molecules are either ionized or excited by irradiation. On delivery of an electron the water radical is ionized positively and decays to reactive ·OH-radicals. The released electron is solvated and can combine with H^+ to form H·-radicals. The excited water molecule decays in ·OH- and H·-radicals. Further steps involving reactive intermediates occur, depending on the radiation quality and on the oxygen amount. ·OH-radicals oxidize, while H·-radicals and e^-_{aq} reduce. In the presence of oxygen, peroxyl radicals can be formed. The simplest peroxyl radical is the superoxide radical ion $O_2^{\cdot}$ that can be formed in normal metabolic processes. The peroxyl radicals enter a chain reaction, in which e.g. hydroperoxides are formed[86].

Radiobiochemistry and DNA damage

Important consequences of the physical-chemical effects are changes in biomolecules and cell structures. Damage to nucleic acids (DNA and RNA), central and indispensable biomolecules, is particularly significant. Irradiation leads to different changes in the double-strand nucleotide chain of the DNA:

- single strand breaks (SSB) or double strand breaks (DSB);
- damage to the bases;
- damage to the sugars;
- intra- or intermolecular crosslinks
- etc.

The changes can be connected with each other. Thus damage to a sugar or the loss of a whole nucleotide can lead to a single strand break. If two opposite SSB happen simultaneously, a double strand break is the result. The two SSB can be directly opposite each other or separated by up to 16 nucleotide pairs. In vitro studies showed a differential radiation sensitivity of the bases with the following order: thymine > cytosine > adenine > guanine. Irradiation of the DNA within the living organism shows a rather different pattern: packaging of the DNA with proteins into chromatin leads to the formation of DNA-protein crosslinks. Multiple lesions of the bases can occur without a strand break, etc. (more in ref. 36).

The DNA damage can be repaired, and only a fraction finally results in permanent damage. In irradiated lymphocytes 70% of the single strand breaks were repaired within 3 min. Double strand breaks are also repaired but to a lesser extent.

Four major repair mechanisms of DNA are known[53]. Photoenzymatic recovery (mainly after UV irradiation) works by monomerization of dimers that were induced by irradiation. Excision repair is a multistep process: first the damage is recognized and excised, then during de novo synthesis of the DNA it is repaired using ligases. Post replication repair is carried out by complicated reactions after DNA replication. In SOS-repair, repair enzymes and repair processes are induced by irradiation. The repair can lead either to an error-free original state or, as misrepair, to the introduction of errors, known as mutations. Besides nucleic acids many other biomolecules, such as enzymes, are affected by irradiation[86]. The influence of radiation on substances and structures connected with the processes of life is of increasing interest (fig. 2). For example, cytokines, that are involved in the process of cell-division[65], are blocked by irradiation[20,66]. Signal transduction can be stimulated by a radiation-induced activation of protein kinases and/or the gene expression can be enhanced[38].

Genetic changes (mutations) in germ and somatic cells

By the process of DNA change mutations of the genetic material occur, such as chromosome aberrations (breaks, translocations, fragment-losses etc.) or point mutations (bases changes). The radiation-induced mutation rate in germ cells depends on their state of development and their sex. Immature stages display more radiation-induced mutations than e.g. mature sperms and spermatogonia. Female mammalian germ cells display fewer mutations than male (have a greater repair capacity). Dilution and fractionation of the dose lower the mutation rate. Environmental factors like oxygen, a sensitizer, and the quality of the radiation influence the number of the radiation-induced mutations (more in ref. 32). Practically all facts about genetic damage to the germ cells originate from experiments with small mammals and *Drosophila*. In contrast no clear data resulted from the large epidemiological studies on the survivors of Hiroshima and Nagasaki. In somatic cells similar mutations happen which can, for example, be the starting point of cancer. It is possible to ascertain radiation-induced chromosome mutations within blood cell cultures by stimulating the cell division of lymphocytes so that their chromosome mutations become apparent. This method offers a biological radiation dosimeter[23].

Cellular radiobiology

In the irradiated cell a diversity of reactions happens, such as biochemical changes, membrane disturbances, morphologic disturbances, mutations, reversible and irreversible delay of the cell division, and cell death. Cell death can happen directly or only after cell division (s) = reproductive death, caused by chromosome damages. The cell cycle is divided in terms of DNA-synthesis[46] into the following intervals: G_1-phase = presynthetic interval, S-phase = synthesis phase, G_2-phase = postsynthetic interval. It is followed by mitosis (M). If the cell stops dividing, it rests in the G_0-phase. The use of in vitro irradiation of cell culture[73] has produced an abundance of information. In relation to cell death, the cells are most sensitive in the late G_1- and above all in the G_2- and M-phase. The progression of the G_2-phase to mitosis is blocked for a shorter or a longer time according to the radiation dose. During this blockage time the cell and chromosome damage may be repaired. In fact, mutants in which the irradiation causes no G_2-delay are more sensitive to irradiation than normal cells[76].

Radiation induction of apoptosis

Apoptosis is programmed cell death, a cellular self-destruction, accompanied or induced by an irreversible DNA-fragmentation carried out by endonucleases. Often apoptosis is equal to interphase death. It is normally typical for embryonic development, T- and B-cell maturation, and endocrine-induced atrophy. Cancer cells can grow because they do not activate apoptosis. The promotion of apoptosis as irreversible cell damage would be of particular interest for cancer therapy. In fact, radiation induces apoptosis, especially in lymphocytes and lymphomas[62]. To be able to induce apoptosis by radiation (see Sauer in this issue), the presence of the tumor-suppressor gene p-53 is necessary, which is also required for apoptosis in non-irradiated tumor tissues[58].

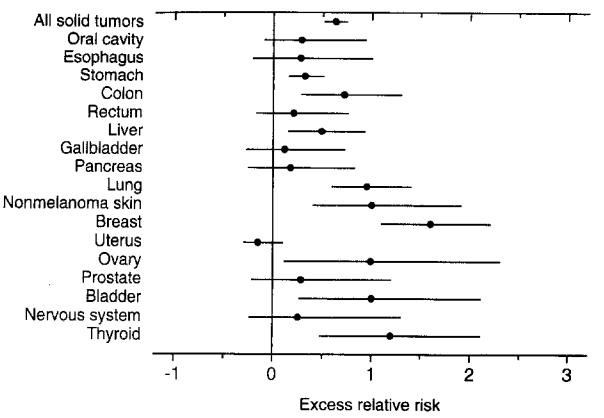

Figure 3. Incidence of solid tumors in A-bomb survivors (1958–1987). Excess relative risk at 1 Sv (RBE 10) and 95% confidence interval. (From Thompson et al. 1994[79], with permission).

Radiation-induced cancer

Practically all organs of man can deteriorate malignantly after irradiation. It was noticed early that small doses of radiation, e.g. in radiologists, induced leukaemia. This phenomenon was observed only in radiologists who had begun to work before 1920 (ref. 17). To estimate the important relation between dose and effect there are some groups suitable for epidemiological studies e.g.

- survivors of the nuclear bomb explosions of Hiroshima and Nagasaki
- irradiated Morbus Bechterew-patients
- children with irradiation of the thyroid gland
- irradiated *Tinea capitis* (fungus illness of the scalp) patients
- tuberculosis patients who were frequently examined by X-ray
- uranium mine workers (see Reinhardt and Gast in this issue)
- patients who had been irradiated radiotherapeutically

The different organs are of different sensitivity to radiation-induced cancer. In figure 3 the frequency of solid tumors in survivors of the nuclear bomb explosions of Nagasaki and Hiroshima is presented. The resulting mortality can also differ, for instance thyroid gland carcinoma leads to death only in a small percentage. Most of the solid tumors display an average minimal latency time of 10 years, while the minimal latency time of leukaemia is only 2 years. Cancer is also induced by incorporated artificial and natural radionuclides. Incorporation of radioiodine in the thyroid gland can induce

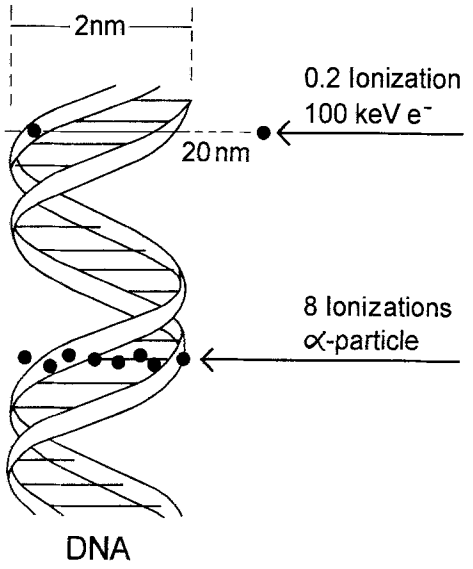

Figure 4. Ionization tracks of low and high LET radiation in DNA.

cancer. Children are especially endangered, which can be seen in investigations on those who had been exposed to radioactive fall-out in 1954 on the Marshall islands[16]. For studies of Chernobyl, see below. Nowadays radon represents a very interesting case. When inhaled radon can cause lung cancer, as shown by the investigations of miners in Schneeberg and Joachimsthal[74] (see Reinhardt and Gast in this issue).

Damage to the embryo and the fetus

As with other teratogenic agents, the different developmental stages react differently to ionizing radiation. In relation to cell death blastogenesis (preimplantation period) is the most sensitive stage, which reacts to as little as 0.5 cGy. During organogenesis the death rate decreases. However the number of deformations and growth changes increases dramatically, while certain anomalies display peaks in sensitivity. Irradiation in the fetal period drastically decreases the number of deformities[31,32,63]. In humans after low-dose irradiation during organogenesis disturbances of the central nervous system are most prominent. So the probability of severe mental retardation is 0.4% per cGy (spontaneous damage 0.8%)[70], according to investigations of children who had been irradiated in utero by explosions of nuclear weapons. There are analogous investigations on intelligence[84]. The child in utero is also very sensitive to radiation-induced cancerogenesis, as it was observed e.g. with children[77] who had been exposed to irradiation during the radiodiagnostic examination of their mothers.

Dependence of the irradiation response on the quality of the radiation (LET)

According to the nature of the radiation the energy is distributed differently in the irradiated material (fig. 4).

Table 3. Radiation weighting factors (ICRP 1991[49]).

Type and energy range	Radiation weighting factor
Photons, all energies	1
Electrons and muons, all energies	1
Neutrons, energy	
< 10 keV	5
10 keV to 100 keV	10
> 100 keV to 2 MeV	20
> 2 MeV to 20 MeV	10
> 20 MeV	5
Protons, other than recoil protons, energy > 2 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

Heavy particles leave a dense ionization track behind, while fast light particles ionize sparsely. The spatial distribution of the energy loss along the passage of a particle is described as linear energy transfer (LET), measured in keV/μm (see Roth in this issue). The number of the ionizations per distance (ionization density) is proportional to the LET. In all fields of radiobiology a strong dependence of the biological effect on the LET is shown, which is described by the relative biological effectiveness (RBE). It is widely observed that a high LET radiation preferentially produces irreparable primary effects and therefore qualitatively differs from a low LET radiation. The RBE increases with increasing LET up to values of 100 keV/μm and decreases again afterwards. For the biologically effective equivalent dose (unit: Sievert = Sv) the radiation-weighting factor is used, which represents an average value, of the respective radiation quality obtained from different RBE-values (table 3).

Recovery processes and dependence of the radiation effect on the temporal distribution of the dose

Recovery processes play a decisive role in the extent of the radiobiological effect. As already mentioned only a fraction of the original damage persists. The repair mechanisms available are used or new ones are induced. In the radiobiological chain of effect (fig. 1) individual recovery processes can occur on the physical-chemical level, as well as on the biochemical and the cellular level. Using survival curves of irradiated cells in culture one can study the effect of the repair. Exponential cell survival curves indicate that the reactive system possesses a very vulnerable range where a single radiation event leads irreversibly to inactivation. Sigmoidal curves show that in the low dose range a large proportion of the cells can survive. In a medium dose range a so-called shoulder is formed, which is attributed to the fact that the cells are damaged sublethally and can recover. At higher doses the curve bends more steeply (more in ref. 5). The possibility of repair indicates that the temporal distribution of the radiation dose (concentrated or diluted, singularly or fractionated) has a large influence on the extent of the radiation effect. A diluted or fractionated application of sparsely ionizing radiation

shows less effect than a concentrated single one. On the contrary for a high LET radiation, dilution can cause the opposite effect. This is caused by the fact that with concentrated high LET radiation a saturation effect occurs. Dilution or fractionating result in a subdivision of the energy amount into subunits, whose effects add up. For radiation protection the dose-reduction factor for dilution and fractionating of sparsely-ionizing radiation is relevant. It is estimated for genetic damage at 3 and for leukaemia-induction, 2.

Interaction of radiation with other factors

The radiation effect depends on different environmental factors, like temperature, biochemical environment, and above all the presence of oxygen. It was ascertained early that oxygen sensitizes, mainly by the production of reactive oxygen products. It was observed in 1934 (ref. 18), that in animal tumors the effect was lowered by irradiation in a nitrogen atmosphere. Since then the oxygen effect (expressed by the term OER = oxygen enhancement ratio) has been confirmed in many systems. The OER is high for a low LET radiation and lower for high LET radiation.

Further chemical and biochemical agents can enhance (=sensitizers) or reduce (=protectors) the radiation effect. For radiotherapy, sensitizing agents for the anoxic cells were found[1] in electron-accepting substances like Ro-07-582 (misonidazole) and etanidazole. Recently it was shown[39] that inhibition of protein kinases using sangivamycin and stauroporine can sensitize human tumor cells to radiation. According to the authors they represent a new class of sensitizing agents. Numerous agents, such as cyanide, cysteine and further sulfhydryl compounds were found to protect against the radiation death of small mammals. At the Walter Reed army hospital more than 3000 compounds were synthesized which should protect the population and the army with as few side-effects as possible during a nuclear war. Among others WR-638, WR 2721 and WR 1607 were produced, which are used as protective agents for healthy tissue in radiotherapy.

As a physical sensitizing agent, hyperthermia is still relevant in radiotherapy, presumably sensitizing by an inhibition of repair.

The radiobiological basis of radiotherapy

The clear aim of radiotherapy is the destruction of the malignant tissue and the protection of the healthy tissue (see Birkenhake and Sauer in this issue). The inactivation of the proliferating tumor cells determines the efficiency of a radiotherapy, but the radiation reaction of the healthy tissue finally limits the success of therapy. Different effects on healthy and malignant tissues were achieved first of all with the help of fractionation. The selective irradiation of the malignant tissues is particularly significant; for more deeply seated tumors the physical depth dose-curve is essential. To limit radiation exposition only to the tumor the exact localization of the target area must be known. This is facilitated today through progress in imaging processes like computer tomography and NMR (nuclear magnet resonance). With their help the correction of non-homogeneous radiation absorption is also facilitated. Localized irradiation is possible through radionuclides (see Rösler in this issue), which are stored in the malignant tissues, and irradiate locally through their decay such as radio iodine in the thyroid gland. The employment of radioactively-marked clonal antibodies is a further possibility for selective radiotherapy.

Radiation sensitivity of tumors

Leukemia, lymphoma, thymoma, seminoma as well as undifferentiated carcinomas or sarcomas are considered radiosensitive. Somewhat less radiosensitive are basal cell and squamous carcinomas. Adenocarcinomas are moderately radiosensitive. The really radioresistant tumors are liposarcoma, neurofibrosarcoma, osteosarcoma, parotis tumor and chondrosarcoma. Different factors determine the radiation sensitivity or radiation resistance of the tumors:

- Presence of hypoxic cells. Absence of oxygen means less radiation effect.
- Reoxygenisation as a consequence of the shrinking of the tumor and the better blood supply of the tumor, or migration of hypoxic cells to regions with more oxygen.
- Tumor size. The smaller the tumor the more radiosensitive it is.
- Repair capacity. The greater the repair capacity of the healthy tissue the greater the success.
- Cell kinetics. Slowly growing tumors are mostly radioresistant.
- Doubling times. Short doubling times are observed in radiosensitive undifferentiated tumors.
- Proportion of cells in radioresistant growth phases. In differentiated radioresistant tumors most cells are in the radioresistant G_0-phase.
- Differentiation stage. Undifferentiated carcinomas are more radiosensitive.
- Reaction of the healthy tissue.
- State of health and age of the tumor carrier. For example, anaemia can lead to increased radioresistance.
- Inhomogeneity of dose.
- Radiation quality (see below).

For a long time a scheme for an optimal fractionation, including different determining elements like reoxygenisation, cell kinetics of the normal and malignant cells, repair capacity, was sought. Diverse formulae such as the Ellis formula, were developed. These, which considered the total dose, the fraction number and the total

time of the treatment, usually only looked at early reactions. The so-called α/β relationship differentiates between early- and late effects. However, experience has proven to be the best teacher.

Sensitizers and protectors

As a sensitizer hyperbaric oxygen therapy was introduced, however with some complications. As already discussed above, there are some chemical radiation modifiers; sensitizers should be used for the tumor cells and protectors for the healthy tissue. Different clinical studies are underway. The combination of radiation and chemotherapy appears to lead to an improvement in healing some tumors (like anal carcinoma). It requires a large amount of medical experience and very careful supervision of the patient under the therapy. The hyperthermia is a good physical modifier with utilization of microwaves, infrared or ultrasound.

Choice of suitable radiation type

In addition to conventional X-rays and cobalt-60-gamma rays, other kinds of radiation are used for the optimization of the radiotherapy. The goal is to achieve the maximum, limited energy absorption in the tumor area, using an increased LET to damage the malignant cells selectively and more effectively. The transit ion curves for different radiation kinds are completely different, and normal tissue is affected differently. Furthermore, densely ionizing radiations with a high LET beside their high relative biological efficiency, offer certain advantages through a low OER. They are not dependent on the presence of oxygen and also destroy anoxic cells. The effect of high LET radiation is more independent of the developmental phase of the irradiated tissues, and the repair of the radiation damage is inhibited.

Radiation kinds, with either a good transit ion curve and/or a high LET

High energy electrons and ultrahard X-rays. The transit ion curves are especially favourable for deep-seated tumors, and different tumor types are treated preferentially with these radiations.

Neutron therapy. The transition curve is not especially favourable; on the contrary, the fast neutrons distinguish themselves through a high LET and with it a low OER. For tumors with a high proportion of hypoxic cells they might be highly effective. Clinically their advantage has not been confirmed in all studies.

Pion therapy. The negative pions have an excellent depth dose curve and a high LET. At the Paul Scherrer Institute (PSI), good results were achieved with the piotron (60-radiations applicator).

Protons. Protons are distinguished by an excellent transit ion curve and a calculable distribution of the energy on a target volume. Their RBE might indeed be only somewhat more than 1. Protons with energies of up to 100 MeV were used successfully in the therapy of choroid membrane melanomas. Protons with energies between 150 MeV and 300 MeV have been used at different places, including the PSI, for deep-seated tumors.

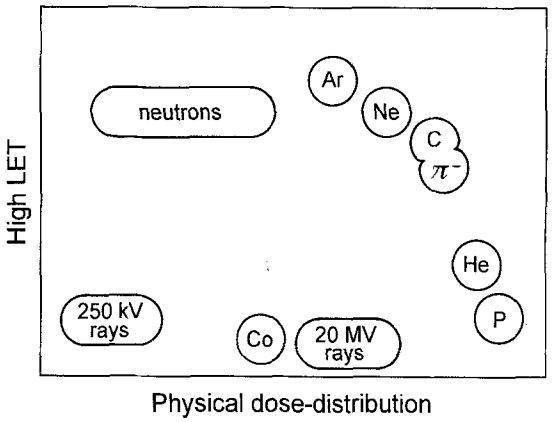

Figure 5. Physical dose distribution and high LET gains of different radiations. (After Fowler 1981 (ref. 27)).

Heavy particle therapy. The physical dose distribution of irradiation with heavy particles can be adjusted to optimal radiotherapeutic conditions. Since however the energy of the heavy ions must be sufficiently high to achieve the necessary effect, up to now radiotherapies with heavy particles could be accomplished only with the Bevalac in the Lawrence Berkeley laboratory in USA. Soon heavy ion therapy will also be possible in Darmstadt, Germany.

Neutron capture. Thermal neutrons are easily caught by the non-radioactive boron-10. Boron or boron compounds are stored selectively in the tumor and then irradiated with low-energy (or thermal) neutrons. This treatment yields a nuclear reaction and a high LET radiation consisting of alpha particles and recoiling Li-7 nuclei. The radiotherapeutical success must be confirmed.

In figure 5 the advantages of the different radiation types are assembled. Further data on radiobiological basis of radiotherapy can be found in refs 32, 37, 68, 83.

Radiobiological basis of radiological protection

The aim of radiological protection is to provide an appropriate standard of protection for humans without unduly limiting the beneficial practices giving rise to radiation exposure. Radiological protection was limited initially to somatic damage to individuals (radiologists, physicists, engineers), but had spread by 1927 to include genetic damage. With the discovery that low doses of radiation can induce cancer, somatic damage was considered further, and today not only the workers who are occupationally exposed but also the general population (like patients with radiodiagnostic burdens, those in the vicinity of nuclear power plant accidents or subject to

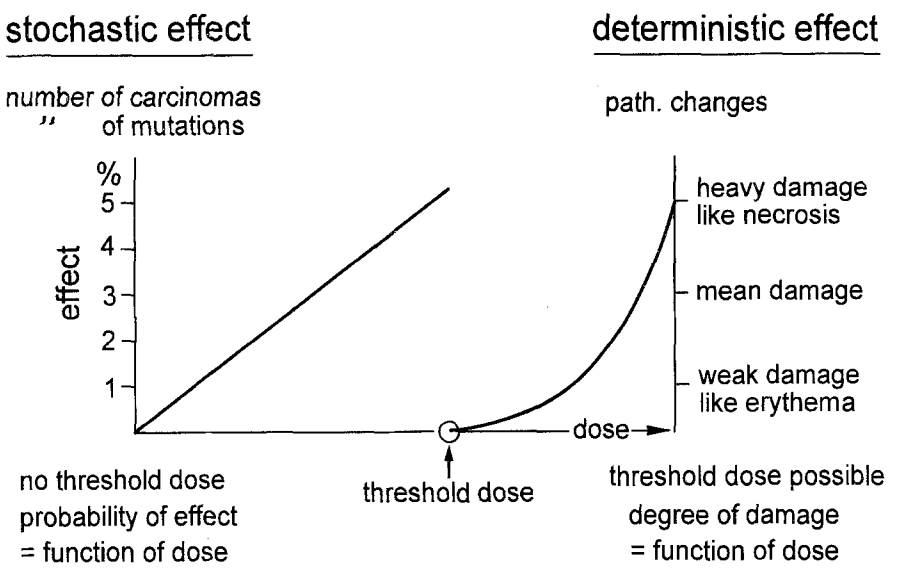

Figure 6. Deterministic and stochastic effects.

naturally increased radiation exposure) are considered in radiological protection (see Roth in this issue).

Deterministic and stochastic effects

For radiological protection it has proven useful to distinguish between deterministic and stochastic mechanisms of radiation effect (fig. 6). Deterministic damages are distinguished by a threshold value in the dose effect relation, under which no damage is to be recorded. Their severity (e.g. loss of organ function) is a function of the dose. All pathological reactions to the irradiation, like skin reactions, bone marrow damage, blood count changes, cataract induction, fibrosis of lung, human radiation syndrome are deterministic. The size of the irradiation area and the temporal distribution of the dose play a decisive role. Both animal experiments and human reactions after therapeutic irradiation[48] are used to estimate threshold doses.

In contrast to the deterministic mechanisms stochastic damages display no threshold dose, and the probability of their appearance is a function of the dose. In this group are included cancer induction and hereditable genetic effects.

Evaluation of risk factors

For recommendation of limits in radiological protection, it is necessary to estimate the stochastic risks. Baseline data for cancer risk come mainly from the epidemiological studies on the survivors of the nuclear explosions of Hiroshima and Nagasaki. Since however only doses over 200 mSv show a statistically significant increase in the cancer risk, the effect of smaller doses must be extrapolated from the damage curves, which thus depends on the choice of the curve form. For cancer induction (with the choice of a linear dose effect curve and the multiplicative projection model), an occupationally-exposed adult person is estimated to have a probability of a cancer death for low doses and dose rates of 4×10^{-2} Sv^{-1} (4 cases on 100 per Sievert), for the general population is 5×10^{-2} Sv^{-1}. For an estimate of the genetic risk experiments with animals are used, since significant data about a dose-effect relation of germ cell mutations in humans are missing. For severe genetic damage an estimate of 0.8×10^{-2} Sv^{-1} is given for the adult occupationally-exposed population, for the general population it is 1.3×10^{-2} Sv^{-1}.

Dose limits

The ICRP 1991 (ref. 49) recommends for occupationally-exposed groups a limit to the effective dose of 20 mSv per year, averaged over 5 years (100 mSv in 5 years), with the further provision that the dose in any single year should not exceed 50 mSv. The limit for the general population per year is 1 mSv (see Roth in this issue). To avoid deterministic effects for the occupationally-exposed group dose limits for the lens of the eye of 150 mSv, for the skin of 500 mSv and for hands and feet of 500 mSv are recommended.

Radiation effects in low dose range: hormesis and adaptive response

As with other toxic agents the effect of small doses of ionizing radiation is detectable with difficulty. The radiobiological effect chain is complex and modifiable. Theoretically there is no doubt that the smallest radiation quantities can lead to mutations and can also be responsible for cancer induction. However the primary events can be reversed through repair processes. It is even possible that the irradiation induces repair systems, producing a more viable individual. Positive effects of small radiation doses are possible. This stimulation by radiation is seen as hormesis (stimulating effect of small doses of agents, which are in higher doses toxic) or as adaptive response on preirradiation. Early in the history

of radiobiology biopositive effects of small radiation quantities were ascertained, such as a longer lifetime in mice irradiated daily with 0.11 cGy (total 100 cG). An extensive literature study[59] described among other things augmented output of irradiated seeds, growth enhancement of plants, etc. Hormesis was observed in Paramecium and blue algae. If they were shielded from a natural background radiation, then their augmentation was inhibited, which was also neutralized by an exposure of 7 mGy per year again[71]. A stimulation of biochemical and biological processes by small radiation doses can be clearly seen in the so-called adaptive response, in which preirradiation with small doses protects many systems against the damage of a second irradiation. This was shown for ionizing radiation for the first time[69] with the induction of chromosome damage in human lymphocytes. For instance, after preliminary treatment with 0.5 cGy, a following irradiation with 150 cGy induced only half the chromosome damage, which would have occurred without preliminary treatment.

A repair inhibitor (benzamide) prevented the protection effect of the preirradiation. Accordingly, it seems preirradiation stimulates repair systems. This is also valid for the biopositive effect of hormesis. Different processes are possible, like an enhanced removal of radiation-induced radicals through an increase in radiation protectors, a direct stimulation of the repair system, an indirect stimulation with a sensitizitation of receptors, a radiation-induced extension of the time of repair, etc. Does hormesis occur in the lowest dose range for human cancer? The investigations of the survivors of Hiroshima and Nagasaki give no answer. Further epidemiological studies of persons[33], who are exposed to an unusually high natural irradiation, like in Kerala (India), the Rocky Mountains (USA), Switzerland, China and Japan, led to the astonishing result, that in 80% of cases either no difference showed itself in the cancer risk or, in more greatly irradiated areas, the cancer risk was even lower. The question of a generally valid hormesis effect for cancer induction remains unsolved. In other systems, experiments clearly ascertained biopositive hormetic effects and possible enhancement of repair through a preliminary treatment. It would be possible, that through the continuous exposure of living organisms with natural high energy radiation during evolution, cells with a dynamic capacity of repair were selected.

Natural and artificial radiation exposure today; Chernobyl

Inorganic and organic matter have been exposed since the origin of the earth to natural radiation. Since December 1895 the artificial has joined the natural burden.

Exposure from natural sources

Radiation exposure through natural sources comes from:

1) the external radiation exposure through extraterrestrial, cosmic sources and through radiation of terrestrial origin.

2) internal irradiation by radionuclides stored in the body.

Cosmic radiation. For the population of Switzerland the annual radiation exposure (effective dose) through cosmic radiation was 0.34 mSv in 1993 (ref. 6). Most cosmic radiation emerges in our galactic system, some however comes from the sun (see Keller in this issue). The primary cosmic radiation consists of about 90% high energetic protons with energies up to 10^{14} MeV, about 10% helium-4 ions, and few heavy particles, along with electrons, photons and neutrinos. After cosmic radiation enters the atmosphere secondary cosmic radiation emerges, like neutrons, protons, pions, kaons and, as further products, electrons, photons and myons. At sea level the myons are the main particles. We are irradiated our whole life long with about 100 ionizing myons each second. The extent of the cosmic radiation exposure depends on the altitude above sea and on latitude. The internal exposure comes about mainly through cosmogenic radionuclides, which are produced by the cosmic radiation. The effective dose totaled 0.38 mSv for the population of Switzerland in 1993. The radionuclides (mainly tritium, carbon-14, beryllium-7 and natrium-22) can enter the body through inhaling or with food and water and irradiate internally.

Terrestrial radiation exposure. This occurs externally through the gamma rays from the radioactive components of the rocks, which form the material of our buildings. The local geology plays a large role (see Reinhardt and Gast in this issue). For the Swiss population a terrestrial exposure of 0.45 mSv is estimated for the year 1993.

Exposure through radon. Exposure to radon is the most significant element of the irradiation by natural sources of the population of Switzerland, with 1.6 mSv effective dose. It arises mainly from the uranium and thorium radioactivity of the rocks of the ground and of most building materials, as well as of water (see Roth, Reinhardt and Gast in this issue). Through their decay radon originates via radium-220 and radon-222, which can be inhaled as radioactive noble gases. Through their decay further radionuclides originate, such as polonium-218, lead-214, bismuth-214, which can collect on small air particles and are deposited and concentrated after their inspiration into the lungs. The particles decay through their short halflife in the lungs, and damage the superficial cells with their emitted alpha rays. The radon concentration inside houses fluctuates considerably according to the building material, underground, ventilation. The largest values were found chiefly in cellars and ground floors. In Switzerland 3% of the dwelling-houses were measured in 1992 and showed an average radon

concentration of 100–200 Bq/m^3 air; however in 5% of the tested houses, levels exceeded 1000 Bq.

The biologically active alpha radiation involves exclusively the lung and produces possibly lung cancer, while the remaining body remains free of radiation. Today it is one of the main tasks of radiation protection to estimate the lung risk induced through radon. If epidemiological studies on mine workers (e.g. miners of the Schneeberg mines) are used to ascertain the increased risk of lung cancer, then, with an average radon concentration of 50 Bq/m^3 air, about 7% of all the observed lung cancer must be caused by radon exposure[50]. Direct epidemiological studies of inhabitants in highly exposed radon houses are not clear. Whereas a Swedish study indicated increasing lung cancer risk with the radon dose, a Canadian study showed no effect of the increased exposure to radiation[78]. Likewise no significant synergistic effect of smoking was observed in the studies of radon houses. The last word has not been spoken, however, and the Swiss Federal Office for Health, section for radiation protection, recommends as a precaution that buildings with 1000 Bq/m^3 radon concentration should be restored.

Man-made radiation exposure

In the population in Switzerland medical exposure (average 1 mSv effective dose/year) is the most significant form of artificial radiation exposure. Each inhabitant is considered, including those never treated radiodiagnostically or radiotherapeutically. Each radiodiagnostic examination and radiotherapeutic exposure is a partial body irradiation. For a stomach radiograph the total effective dose for a man is about 0.49 Sv, for a woman about 0.56 mSv (somewhat more because of the breast irradiation). At the effective dose the stochastic cancer risk is considered for all organs. The aim of the radiation protection is to keep the radiation burden through the X-ray diagnostics as low as possible ('ALARA' principle).

The further artificial radiation exposure of the population in Switzerland through fallout of exploded atomic bombs, the Chernobyl accident, nuclear reactors, industry and hospitals, and other small sources, totals for the year 1993 an effective dose of 0.2 mSv.

The total dose for the Swiss population through natural and artificial exposition totals per year (1993) on average up to 3.97 mSv.

Chernobyl accident

The largest disaster in a nuclear reactor occurred in April 1986 in Chernobyl, Ukraine. The total amount of the released radioactive material is estimated[85] to have been 1–2 EBq (10^{18} Bq), the principal radionuclides being I-131 (630 PBq, 10^{15} Bq), Cs-134 (35 PBq), Cs-137 (70 PBq). In contrast to I-131 with its short radioactive halflife of 8 days, Cs-134 with a radioactive halflife of 2 years and Cs-137 of 30 years are long-lived radionuclides. The radionuclides contaminated the local environment or were driven in the atmosphere and then caused world-wide contamination.

Radiation exposure of the population near the reactor. The greatest exposure was of the fire fighters and operators in the reactor, with some receiving 25 Sv. About 115 000 inhabitants were relocated from a 30 km exclusion zone surrounding the reactor with estimated doses of less than 0.25 Sv up to 0.3 and 0.4 Sv. For a population of about 270 000 outside the 30 km zone, 37 mSv was estimated in the year after the accident and 23 mSv in the subsequent 2 years.

Biomedical implications. Only high doses are expected to produce deterministic *irreversible* early damage, which actually appeared in the fire fighters and operators in the reactor. 29 persons died through early radiation sickness (threshold dose = 1 Sv). More weakly irradiated persons showed a reversible decrease of the lymphocytes, infections and hemorrhages. A large international study[47], which was presented in 1991 in Vienna at a Symposium of the International Nuclear Energy Agency, dealt exclusively with moderate radiation exposure more than 30 km from the reactor, in areas with more than 185 kBq caesium-137/m^2. No radioinduced health damage, like for example heart vessel anomalies, cataracts, damage to the immune system, thyroid gland anomalies etc. were observed. Likewise no stochastic damages such as leukemia or thyroid carcinoma were seen. Recently in areas of Byelorussia with a slight radiation exposure of 1.47–7.35 mSv disturbances of the immune system were discovered[12]. Little is known about the state of health of the so-called 600 000 liquidators, who had been involved from time to time in the clean-up operation of the reactor. Their radiation exposure might total a maximum of 0.25 Sv. Five years after the accident some of them showed a 4-fold increase in chromosome aberrations in the lymphocytes[54]. While stochastic damage like cancer induction did not appear early (because of the long latency time of the tumors), there are now reports of an increase in thyroid anomalies and cancer. Children are especially endangered, above all in the region of the city of Gomel, Belarus, which was exposed to a radioactive cloud. It was observed in 1990 and 1991 that children had about 20 times more thyroid carcinomas[75]. The burden to the thyroid gland through radio iodine totaled an average of 3.1 Gy. In districts in southern Belarus[24], 50–150 km from Chernobyl, an increase in thyroid anomalies and carcinomas was also found in children and adults. Eight years after the accident Ziborowski[88], chief physician at the Ukrainian Institute for Pediatrics, Obstetrics and Gynecology in Kiev, observed more still-births, an increased mortality in the new-born and generally more death in children of all age groups in the heavily contaminated areas. This damage to health is by no means a consequence of the radiation alone. Demographic,

social and economic changes played a role, along with psychic stress.

Radiation exposure from Chernobyl in Switzerland. According to the meteorogical conditions individual areas were contaminated differently. For the average population in Switzerland a dose burden was calculated in the first year after the Chernobyl accident of approx. 0.15 mSv. The additional dose in the following years (contamination with caesium) might total about 0.5 mSv. From it a possible increase of the cancer risk is at most 0.021%.

Space radiobiology

The radiobiology of space deals with the biomedical effect of cosmic radiation in interaction with other space factors. This analysis is useful to basic research of a unique radiation environment, and to the evaluation of health risks of the cosmonauts. Cosmic radiation, which was discovered in 1912 by Hess[43], consists primarily of a mixture of protons, fewer electrons and positrons, alpha-particles, and about 1% heavier nuclei. The latter component comprises the so-called HZE-particles of charges $Z > 2$ and great energy.

Effect of the HZE-particles (heavy ions)

Although they only contribute 1% of the flux of galactic cosmic radiation they are predominantly involved in the biomedical effect of cosmic radiation. Their effect might be qualitatively different from other radiation kinds, e.g. because of the compact energy concentration and their probable suppression of repair events. Their energy is high enough to get through the shielding material of the spacecraft or a spacesuit. Interestingly enough they were seen by astronauts (first during the Apollo 11 mission and then in other flights), who observed light flashes in the dark, as the HZE-particles penetrated the eyes of the astronauts and excited the retina. In numerous experiments the biological effect of HZE-particles was tested on different systems. Mostly convincing are the tests made with the so-called Biostack concept[13], in which the biological effect is correlated with the passage of a HZE-particle. Track detectors are sandwiched between layers of biological material, like bacterial spores, plant seeds, embryonic systems. The most sensitive appear to be the embryonic systems of insects[45], in addition to mutation and tumor induction (Bioblock method).

Interaction with microgravity

Different factors of space flight, like acceleration, vibrations and above all the microgravity in space, can influence the radiation effect. In the Biostack experiments, it could be shown that the microgravity interacts in a synergistic manner, e.g. enhancing considerably the radiation-induced anomalies in the development of insects[45].

Radiation protection for astronauts

The exposure to radiation of astronauts depends on the duration, altitude and inclination of the flight, on the solar cycle, on the anomalous sun events, and several other parameters[8]. So for the mission D1 (ref. 14) at an inclination of 57 degrees, an altitude of 324 km, with a radiation mixture with a medium dose rate of 216 μGy/d, a biologically effective dose rate of 479 μSv/d (radiation weighting factor for HZE-particle = 11.9) was calculated. The dose limits (radiation protection) for astronauts have been determined from the risk to agriculture and construction workers with exposures of 0.5 Sv/year.

Outlook on future developments

Radiobiology should work, as always, in parallel with basic research in the service of the biomedicine (radiation risk, radiological protection and radiotherapy). Radiobiology should profit from recent progress in molecular biology. The meeting between radiobiology and cellular molecular biology is a beneficial one[15]. On the other hand, modern radiobiology should also work more with in vivo experiments and use in vitro experiments as instruments and not as models[51]. Radiation-induced DNA damage is in vivo in part unlike the in vitro events[36,86]. The widely-accepted statements that the biological effect depends on many factors, such as physiological milieu and genetic background, forbid a one-sided analysis.

The relationship between damage and repair is a main topic. Repair processes dominate in terms of radiation protection, such as the effect of small doses. In vivo experiments show, that the primary processes necessary for cancer induction are modified through repair. It is possible that radiation-induced repair processes reduce 'normal' damage rate and so become biopositive. These hormetic effects and the adaptive response demand further investigation. For radiotherapy biomolecularly indicated factors as protectors of the repair processes in the healthy tissue and inhibitors of repair, as sensitizers of the effect on tumor cells, are particularly important. Genes, their mutation, expression, and involvement in carcinogenesis, play a central role. An example is the radiation-activated induction of tumor necrosis factor[38], which results through an increase in gene expression. The radiation-induced increase in protein kinase C presumably causes this increase in gene expression. Tumor necrosis factor has a cytotoxic effect on tumors. In gene therapy, radiation could be used to activate the expression of exogenous genes that encode cytotoxic proteins[87]. Carcinogenesis begins with genetic alterations. About 100 proto-oncogenes are known and about 12 tumor suppressor genes. Their mutation can be responsible for the cancer induction. Since different tissues are differently sensitive to radiation-induced

tumors[79], it would be interesting to test the radiation tumors in the presence of mutated proto-oncogenes or tumor suppressor genes.

The pairs 'damage and repair' as well as 'gene and soma' should not be considered as opposites but as complex units. Such an approach might lead the radiobiology of the future to greater success.

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