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Radiobiological fundamentals in radioepidemiology and radiation protection

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General radiobiology has a threefold importance: firstly, radiation is a convenient tool to study fundamental processes of life; secondly, radiobiology serves as a basis for the clinical application of radiation, and finally, radiobiology plays a role in radiation protection. Concerning the first aspect, radiobiology as an interdisciplinary research field deals with various experimental studies from the molecular to the organism level. The aim of these activities is to understand the complex processes and mechanisms in the chain of events starting with the absorption of energy and ending with the final biological effect. From the point of view of clinical radiobiology and radiation protection, biological changes resulting from ionizing radiation must be studied in order to maximise the benefits of its use while at the same time protecting human beings and other organisms from its harmful effects[1].

During the almost 90 years that have passed since Wilhelm Conrad Röntgen discovered "a new kind of ray" an enormous amount of information on radiation effects in living systems has accumulated (see reviews[2, 3]). Major findings, such as the inhibition of cell division, or the description of the different sensitivity of various cell types, were already established in the first decade of this century. The mutagenic effect of radiation, cell-cycle dependent responses, damage to DNA and chromosomes, repair processes, cell transformation, developmental disorders and modification of radiosensitivity are also fundamental phenomena. Although a great deal has been learned about the actions of radiation, two main gaps in our knowledge still remain[4]. One is the identification of critical targets and lesions causing cell death, and the other one is the mechanism of tumor induction.

Radiobiological principles

The chain of events. When radiation energy is absorbed in biological material, excitations and ionizations are produced in atoms and molecules. It is principally the ionization event that causes biochemical changes which may or may not be reversible. As shown schematically in *Figure 1*, indirect or direct action may lead to genetic, chromosomal or other damage, and these cellular effects are starting-points for subsequent biological consequences. The indirect action is mediated mainly by hydrogen and hydroxyl radicals. These free radicals contain an unpaired electron, are very reactive and may lead to lesions in biomolecules and membranes. It is generally accepted that DNA is the principal but not exclusive target for radiation-induced cell death, mutation and transformation[2]. Radicals have a very short lifetime of about 10^{-5} sec before a further reaction (e.g. peroxide formation) or recombination takes place. In the case of sparsely ionizing radiation (X-rays, γ-rays), 60–70% of the damage to DNA results from OH radicals produced by the radiolysis of water.

In the case of densely ionizing radiation (e.g. neutrons or α-particles) direct action, resulting in ionization in the DNA itself, dominates. According to Hall[6], the ionization products of DNA are less well known. Guanine cations and thymine anions are the main forms of radicals.

DNA and chromosomal damage. Studies on irradiated DNA revealed the following types of structural alterations: single strand breaks, double strand breaks, damage to bases, locally multiplied damaged sites, DNA-protein crosslinks, and decondensed chromatin[7]. Further analyses are necessary for the understanding both of the molecular changes mentioned and of the mechanisms leading to the next steps in the chain of biological events. For the three major structural alterations, the frequencies are of the order of 1000 single strand breaks, 40 double strand breaks and at least 2000 base changes per cell and per Gy. Such damage, if not corrected by excision or other forms of repair, may result in chromosomal breaks and aberrations.

Chromosomal abnormalities are divided into three classes: changes in number (e.g. trisomy), breaks and rearrangements. The latter abnormalities consist of unstable forms (rings, dicentrics) and stable forms (translocations, deletions, inversions). Their occurrence is related to the inappropriate joining of two breaks at different sites. Some of these aberrations, like dicentric chromosomes, provide a means for biological dosimetry and risk evaluation. Genetic changes and chromosomal aberrations are accepted as the main causes of cell killing, tissue damage, cancer and other consequences. However, one major process, possibly the most interesting one in radiobiology, counteracts these effects. This is the capacity for DNA repair and cellular recovery. Complex, enzyme-mediated repair systems specifically recognize and remove DNA damage, transfor-

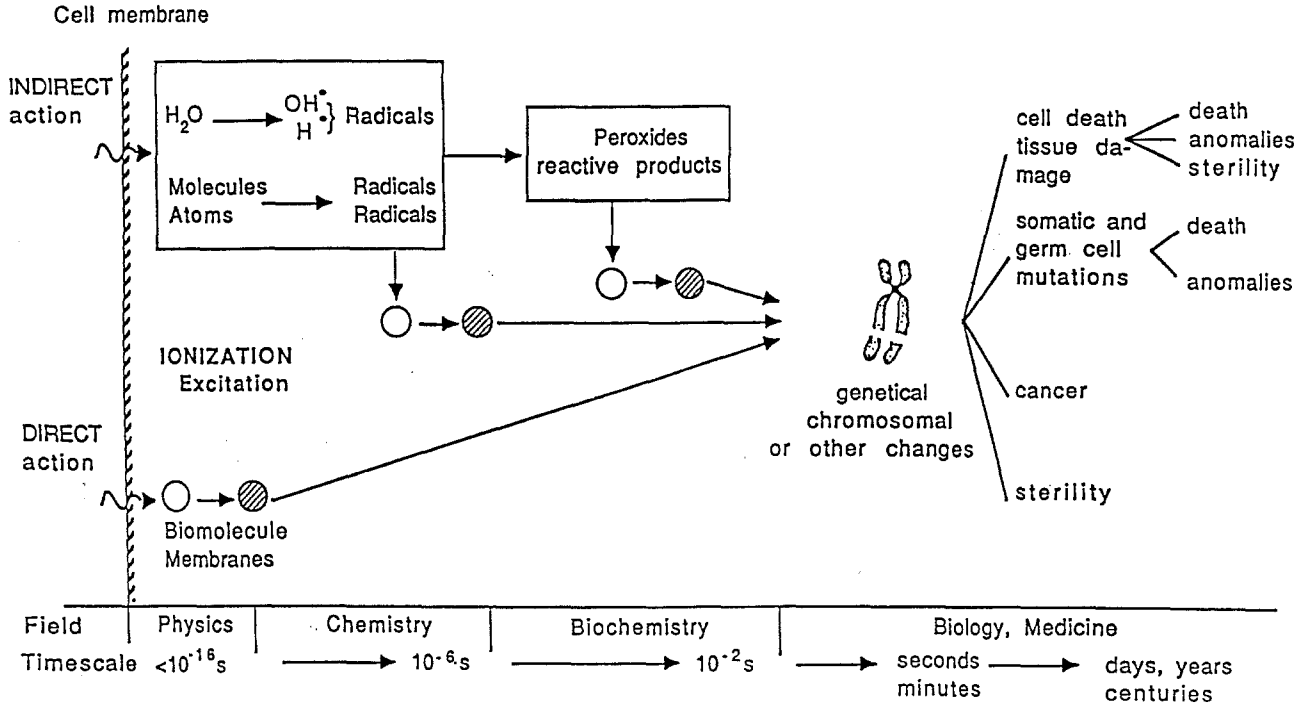

Fig. 1. Chain of events from energy absorption to the final biological changes: The direct and indirect actions of radiation. Adapted from Fritz-Niggli[5].

ming the DNA structure back to its original form. Such repair processes may be error-free or error-prone, depending on the type of damage and various other conditions (genetic factors, age, health status, dose rate, radiation quality). Biological endpoints, as indicated in *Figure 1*, are therefore the net result of both radiation-induced initial changes and subsequent repair processes.

Influencing factors. The biological chain of events including repair may be influenced by various factors, such as dose, dose-rate, spatial dose distribution, cell and tissue sensitivity, and chemical modifiers. For dose-response relationships, the shape of the curve is often represented accurately by a linear quadratic model. It follows that linear interpolation from data with high doses to low doses overestimates the effect per unit dose at low levels. In general, the degree of biological effect per unit dose of low LET-radiation is also reduced when the dose rate is lowered. With the dose and dose rate effectiveness factor (DDREF) either dose or dose rate reduction is described in *Table 1*.

A further fundamental finding is that the biological consequences of irradiation vary with the spatial dose distribution, i.e. with the radiation quality. In order to characterize the quality of radiation, the concept of relative biological effectiveness (RBE) has been introduced. RBE is defined as the ratio of the reference radiation dose (D_r) to the test radiation dose (D_t):

$$RBE = \frac{D_r}{D_t}$$ required for the equal effect

Tab. 1. Summary of Dose – Rate Effectiveness Factors (DREF) for low-LET radiation.

Sources of data		*DREF**
NCRP-Report 64[a]	1980[12]	2–10
UNSCEAR[a]	1986[13]	5
ICRP 1990[b]	1991[1]	2
BEIR V[a]	1990[2] (human leukemia)	2.1
Animal data[a]		
Specific locus mutation		5
Reciprocal translocation		5
Life shortening		4
Tumorgenesis		4

* The factor by which linear interpolation from data obtained at high doses and dose rates overestimates the risk per unit absorbed dose of radiation delivered at very low doses and/or dose rates.

a) DREF: observed values.

b) DDREF: Dose and Dose-Rate-Effectiveness-Factor: defined value.

Generally 250 kV X-rays are used as the reference. RBE depends not only on linear energy transfer (LET) but also on dose, dose rate, biological system and endpoint. For fission neutrons, RBE values between 3 and 200 were found for tumor induction or lens opacification (*Table 2*). Observed RBE values are an important quantity, providing a basis for the quality factors used in radiation protection.

The radiosensitivity of cells and tissues is a central problem in radiobiology and is characterized by two factors: the inherent sensitivity of individual cells and the kinetics of the cell population as a whole. When cell death or cell degeneration is

Tab. 2. RBE_M for Fission Neutrons vs. Fractionated γ-Rays.

Tumor induction	~ 3– ~ 200
Life shortening (due to tumors)	15– 45
Transformation	35– 70
Cytogenic studies	40– 50
Genetic endpoints (mammalian systems)	10– 45
Other endpoints	
Lens opacification	25– 200
Micronucleus assay	6– 60
Testes weight loss	5– 20

ICRU[8]

chosen as the endpoint, oocytes, spermatogonia, neuroblasts and small lymphocytes are the most sensitive cells. The death of single cells is observed in these cell types already after very low doses of radiation of the order of a few cGy. At the other extreme, adult nerve cells survive exposures of several Gy. Most of the sensitive cells suffer a mitotic or reproductive death, i.e. death occurs at a subsequent mitosis after irradiation. Interestingly, oocytes and lymphocytes die in interphase before a cell division begins. The high resistance of adult neurons, in terms of death, may be attributed to the cessation of mitosis and their fully differentiated status (closed static cell population).

Despite the similar radiosensitivity of most other mammalian cells with respect to cell death, tissues differ markedly in their responses to radiation. Much of this variation is due to the different kinetics of the growth of the cell population[9]. Whether a tissue or organ is denoted as sensitive or resistant is dependent on the amount of cell killing, and the ability to compensate for cell loss by proliferation of viable cells. If the radiation dose remains below a certain threshold, the tissue may recover and retain its functional entirety. Besides cell killing a variety of other mechanisms, e. g. membrane alterations or functional changes in the neuroendocrine system, contribute to the so-called deterministic (nonstochastic) effects[1].

As *Figure 2* reveals, there is a further type of radiation effect, namely the stochastic one. In contrast to the mechanisms mentioned before, stochastic effects ensue not from cell killing but from cellular alterations resulting in viable cells capable of further proliferation – controlled or uncontrolled. Induction of cancer and hereditary disorders are two established examples of stochastic effects, whereas mental retardation is not generally regarded as a stochastic effect. Stochastic effects are assumed to be a function of dose even in the low dose range. By definition, there is no threshold[10] and the occurrence of such effects has an increasing probability as the dose increases. Considering the fact that the energy of ionizing radiation is superior to that of chemical bonds within biological targets, alterations in biomolecules and DNA must be expected when radiant energy is deposited in such structures. So, no level of exposure to ionizing radiation can be denoted as ineffective. But, at the same time, no level is uniformly dangerous. Whether changes in exposed cells are harmful or not depends on processes like repair, selection, and

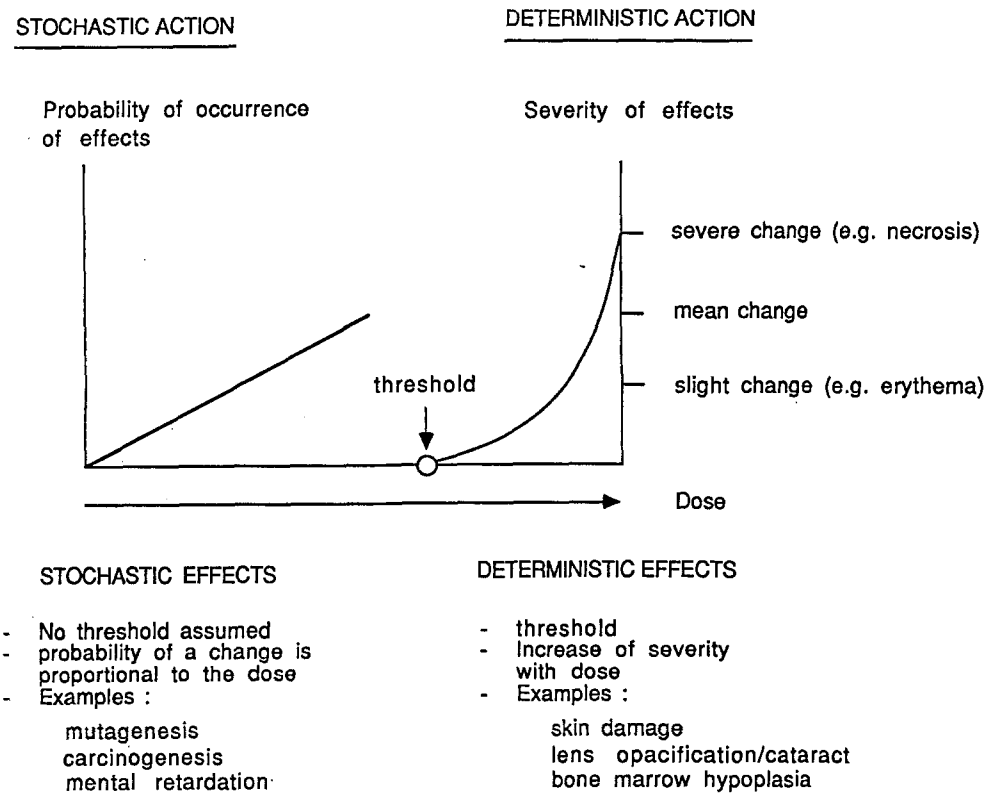

Fig. 2. Definition and nature of biological radiation effects: The stochastic and deterministic mechanisms of action.

elimination of these initial alterations. According to a classification of biological radiation effects, damage to a single cell or a few cells is not necessarily deleterious for the whole organism [1]. However, in the case of harm, a definite detrimental effect is present in an exposed individual (somatic effect) or in its descendants (hereditary effect). This harm may be the result of a disturbed balance between initial damage and repair.

In summary, the hypothesis of a linear, non-threshold dose effect relationship, at least with respect to the induction of cancer and hereditary defects, is justified despite efficient repair processes [2].

More data from experimental and epidemiological sources are needed for a more confident quantitative understanding of low-dose radiation effects. The role of radiobiology in this context is described by Sinclair [11] as follows: "If we want to know more precisely what goes on at the low doses of interest in radiation protection, we must, at present, turn to the laboratory".

Summary

Radiation is a convenient tool to study fundamental processes of life. Biological effects of irradiation may result from indirect actions which are mediated by free radicals (e. g. OH-radicals) or from direct actions which involve ionizations in the DNA and other biomolecules. Damage to the DNA is the principal, but not exclusive target for cell death, loss of reproductive integrity, mutation, cancer, developmental anomalies and other radiobiological effects. Repair of damaged DNA and cellular recovery processes play an essential role in affecting the survival of cells. Dose, dose rate, radiation quality, biological and chemical modifiers also have a pronounced effect upon the extent of radiation responses. The biological effects of ionizing radiation are somatic or hereditary and can further be classified into stochastic and deterministic effects. For radiation epidemiology and protection the stochastic action is more relevant because the probability of an effect is a function of dose, without a threshold. Induction of cancer, hereditary diseases and probably also mental retardation are regarded as stochastic effects.

Résumé

Les bases biologiques de la radioépidémiologie et de la radioprotection

Les rayonnements ionisants représentent un instrument très efficace pour l'examen des phénomènes fondamentaux de la vie. Les effets biologiques d'une irradiation sont le résultat de mécanismes *indirects* (formation de radicaux) ou *directs*, comme par exemple des ionisations de l'ADN ou d'autres molécules. Les lésions dans l'ADN sont considérées comme la principale cause de mort cellulaire et de mutations, de tumeurs et de troubles du développement. Il est important de savoir qu'il existe des mécanismes de réparation cellulaire, capables de restaurer la structure normale de l'ADN, des membranes, et des autres structures cellulaires. Les facteurs déterminants des effets biologiques induits par l'irradiation sont la dose, le débit de dose, la qualité du rayonnement et les substances chimiques. On distingue deux groupes d'effets selon la relation dose-effet, stochastiques et non-stochastiques. Concernant la radio-épidémiologie et la protection contre les irradiations, ce sont les effets stochastiques qui jouent le rôle principal: Ils apparaissent en fonction de la dose et sans valeur seuil. Cela est le cas pour l'induction de tumeurs, de troubles génétiques et des troubles mentaux chez les enfants irradiés in utero.

Zusammenfassung

Strahlenbiologische Grundlagen in Strahlenepidemiologie und Strahlenschutz

Ionisierende Strahlen sind ein geeignetes Werkzeug, um grundlegende Lebensprozesse zu studieren. Biologische Strahlenwirkungen können auf indirektem Weg (via Radikalbildung) oder direkt, durch Ionisationen in der DNS oder anderen Biomolekülen, erzeugt werden. Veränderungen in der DNS werden als Hauptursache bei der Auslösung von Zelltod, Mutationen, Krebs, Entwicklungsstörungen und anderen Effekten betrachtet. Durch Reparaturprozesse können strahlenbedingte Änderungen der DNS, der Membranen und anderen Zellkomponenten auch wieder rückgängig gemacht werden. Dosis, Dosisrate, Strahlenqualität und chemische Substanzen haben einen bedeutenden Einfluss auf die Strahlenwirkung. Je nach dem Verlauf der Dosis-Effekt-Kurve können stochastische oder nicht stochastische (deterministische) Wirkungen unterschieden werden. In bezug auf Strahlenepidemiologie und -schutz stehen stochastische Effekte im Vordergrund, da sie als Funktion der Dosis auftreten, ohne dass eine Schwellendosis angenommen wird. Zu diesen Wirkungen werden die Krebsinduktion, genetisch bedingte Leiden und oft auch geistige Zurückgebliebenheit bei Kindern nach intrauteriner Bestrahlung gezählt.

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