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Radiological Protection: Challenges and Fascination of Biological Research

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Radiological Protection: Challenges and Fascination of Biological Research

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ANMERKUNG DER SCHRIFTLEITUNG
Der folgende Beitrag ist die geringfügig gekürzte Version der „Sievert Lecture", gehalten vom Autor bei der IRPA 12 am 20. Oktober 2008 in Buenos Aires.

ZUSAMMENFASSUNG
Strahlenschutz: Herausforderung und Faszination der biologischen Forschung
Zur Bewertung von Strahleneffekten im niedrigen Dosisbereich (<100 mSv) sind biologische Studien notwendig. In dieser Hinsicht sind DNA-Schäden und ihre mögliche Reparatur, „Adaptive Response", „Bystander Effekte", genomische Instabilität und genetische Disposition des exponierten Organismus sowie die Wechselwirkung dieser komplexen Prozesse sehr wichtig. Die Einflüsse solcher Strahleneffekte auf die Karzinogenese, die ein Mehrschritt-Prozess von Mutationen und Regulation des Zellzyklus ist, werden dargestellt und in Hinsicht auf den Strahlenschutz diskutiert.

SUMMARY
In order to evaluate radiation effects in the low dose range (<100 mSv) biological studies are necessary. In this respect DNA damage and its possible repair as well as adaptive response, bystander effects, genomic instability and genetic disposition of the exposed organism as well as the interplay of these complex processes are of great importance. The implications of such radiation effects on cancer induction which is a multistep process of mutations and cell cycle regulation are investigated and discussed with respect to radiological protection.

Evaluation of the Mechanisms of Radiation-Induced Health Effects

Dose limits in radiological protection are predominantly based on epidemiological studies of cancer and hereditary effects. Such effects have been significantly observed after doses of around 100 mSv and higher. After lower doses the radiation effects are covered within the fluctuations of the "spontaneous" cancer rates. Thus the risk in the lower dose range can only be estimated by extrapolation using the LNT model. Experimental studies are necessary in order to evaluate the mechanisms of radiation-induced health effects and thus to contribute to the understanding and to the dose response of possible effects in the lower dose ranges.

Extensive radiobiological studies have been performed on DNA damage and its possible repair as well as on phenomena like adaptive response, apoptosis, bystander effects, genomic instability and genetic disposition. Such studies give interesting insights into the complex biological processes which occur after irradiation and into their possible contribution to the development of health effects. The interplay of these complex processes is very important. Some of these radiation-induced biological changes can be seen after radiation doses below 100 mSv. Radiosensitive individuals are found with whom smaller dosis can be recognized. The implications for radiological protection are discussed in dependence of the LET of ionizing radiation and of the genetic disposition of the irradiated organism.

Some historical aspects

Soon after the discovery of X-rays in 1895 by Roentgen and of radioactivity in 1896 by Becquerel it was recognized that ioinizing radiation causes biological effects which can be used for the therapy of cancers but which also can be deleterious e.g. damage of the skin and induction of cancer.

Development of a dosimetric system

In order to analyse and judge these effects it was found necessary to develop a dosimetric system. Christen was one of the first who defined a physical dose for X-rays in 1913: "The physical dose or ´rough dose´ is equal to that amount of X-ray energy which is absorbed in a body element divided by the volume of this element." At the 2nd International Congress of Radiology (ICR) in Stockholm the first international dosimetric unit the „Roentgen" (R) was defined and approved as „exposure dose" [1]. Twenty five years later in 1953 at the ICR the „absorbed dose" with the dose unit „rad" was defined (1 rad = 100 erg/g = 0.01 J/kg). Later the equivalent dose with the unit „rem" followed and in 1979 the Conférence Génerale des Poids et Mesures (General Conference on Weights and Measures) introduced the „Gray" (Gy) and the „Sievert" (Sv).

In 1903 Heineke already described the high radiosensitivity of the haematopietic system and especially of lymphocytes; in 1927 Muller observed for the first time mutations in Drosophila after exposure to a toxic agent, namely X-rays, and a linear dose response turned out. Interestingly Muller only found such mutations after irradiation which were also observed spontaneously in these flies. In 1953 Watson and Crick published the double-helical structure of DNA which became and is still of utmost importance for the understanding of biological effects after radiation exposure. In 1958 R. Hill discovered very large differences with respect to radiosensitivity between two strains of E. coli bacteria. For the first time the author assumed that these differences of radiosensitivity are due to changes in an enzymatic DNA repair [1]. These repair processes which have been elucidated during the last decades have proven to be very powerful and efficient processes in order to stabilize the DNA structure with its genetic information during the whole lifespan of an individual.

Over about hundred years and especially during the last decades a tremendous amount of data and fascinating insights into life processes have been obtained for biological radiation effects from experimental and clinical investigations as well as from epidemiological studies [2, 3, 4]. Such knowledge is the biological basis for the system of radiological protection today. For radiotoxicological estimates the knowledge of dose responses is decisive. Radiobiological and clinical studies have shown that the so called "deterministic effects" (acute effects, cataracts, malformations) apparently only occur after radiation threshold doses have been exceeded. These threshold doses are above the dose limits and reference values used in radiological protection (>100 mSv) [5]. In the low dose range (<100 mSv), important for radiological protection, only genetic and carcinogenic effects are expected. The induction of cancer is the dominating effect for the evaluation of radiation risk in the low dose range.

Induction of cancer dominating effect

For these radiation effects a linear dose response without a threshold (the LNT model) has been proposed and used for the extrapolation of radiation risk from high and medium radiation doses to low dose ranges [5, 6, 7]. Experimental and epidemiological evidence has been described for such a dose response but it has also been strongly disputed [8]. There is no scientific proof for the dose response of cancer induction in the dose range below 100 mSv. During recent years a number of biological processes have been studied which may modulate the dose response especially in the low dose range. The discussion will be focussed on these questions in the following.

Epidemiological findings and their limits

The most extensive epidemiological studies after exposure to ionizing radiation are still the investigations of cancer incidence and mortality of the survivors of the atomic bombing in Hiroshima and Nagasaki. With the recent data cohorts of 86.572 survivors with 9.335 cancer deaths and 105.427 survivors with 17.448 primary cancer diseases were analysed which came to more or less the same conclusions [9, 10]:

- Up to radiation doses of 2 Sv the data can be described by a linear dose response curve without a threshold.
- A statistically significant increase of cancer (all solid cancers) is observed after radiation doses >120 mSv.
- The excess relative risk per Gy (Sv) is about 0.47 for persons at the age of 70 years and exposure at age of 30 years averaged over both sexes.
- Women are more radiosensitive than men by a factor of about 1.7.
- Children and adolescents are generally more radiosensitive than adults.
- Strong differences exist with respect to the radiosensitivity between the different organs and tissues.

These studies are the basis from which ICRP derived the risk factor of 5×10^{-2} per Sv for stochastic effects after exposure to low LET radiation in the low dose range with low dose rates

and of 10^{-1} per Sv for high LET radiation.

Quite a number of other epidemiological studies about the induction of stochastic effects and especially of cancer in humans after exposure to ioinizing radiation are compatible with the data from Hiroshima and Nagasaki [5, 7]. This is the case for investigations on nuclear workers [11, 12, 13], for the population at the Techa River exposed to radioactive releases from the Russian fabrication of atomic weapons [14] and for populations living in regions with high background radiation [15]. In all studies no significant increase of cancer induction has been found in the low dose range (< 100 mSv). The data which have been obtained with the studies on the atomic bomb survivors show fluctuations around the linear dose response below doses about 100 mSv (Fig. 1). This can be explained by two possibilities:

No significant increase of cancer below 100 mSv

1. No cancers are induced after exposures to such low radiation doses.
2. Cancers are induced after these low doses but the effect is so small that it is hidden by the fluctuations of the spontaneous occurrence of cancer (Fig. 2).

In Fig. 2 the large fluctuations of the annual cancer rate can be seen which has been observed even with the large population of the U.S.A. and which is represented as the deviation from the average cancer mortality (SEER) over ten years. In comparison to these values the expected cancer mortality after radiation doses (low LET, low dose rate) of 1.000, 100 and 10 mSv is shown. It is obvious that the possible radiation effect of doses < 100 mSv cannot be discovered as the fluctuations of the background cancer rates are larger than the radiation effect in these low dose ranges. An individual cancer which may have been caused by ionizing radiation can by no means be distinguished from cancers which originate from endogenous or other unknown causes ("spontaneous" cancer or background). There does not exist a specific signature for radiation which would make such a distinction possible. The clinical appearance and all pathological, cellular as well as molecular features of radiation induced cancers which have been studied so far do not give any indication for a difference. It appears that the evaluation of the mechanism of carcinogenesis can bring clarification whether cancers can be induced by low or very low radiation doses and how the dose response curve looks like in the low dose ranges. It is a great challenge for radiobiological research to contribute to the solution of these questions.

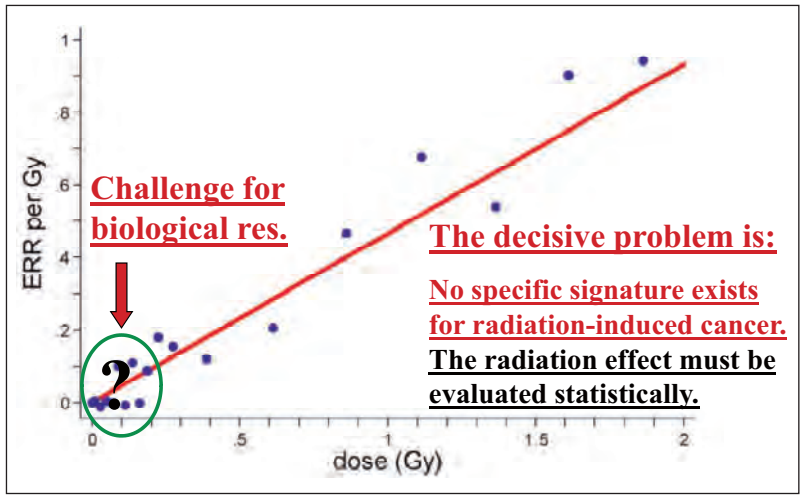

Fig. 1: All solid cancers fitted linear dose response and dose category specific ERR estimates in Hiroshima and Nagasaki (RERF 2008); www.rerf.or.jp/

DNA damage and Repair

The present view is that the genome of a cell, the DNA, is the primary target for ioinizing radiation in order to induce stochastic effects including cancers and there is strong experimen-

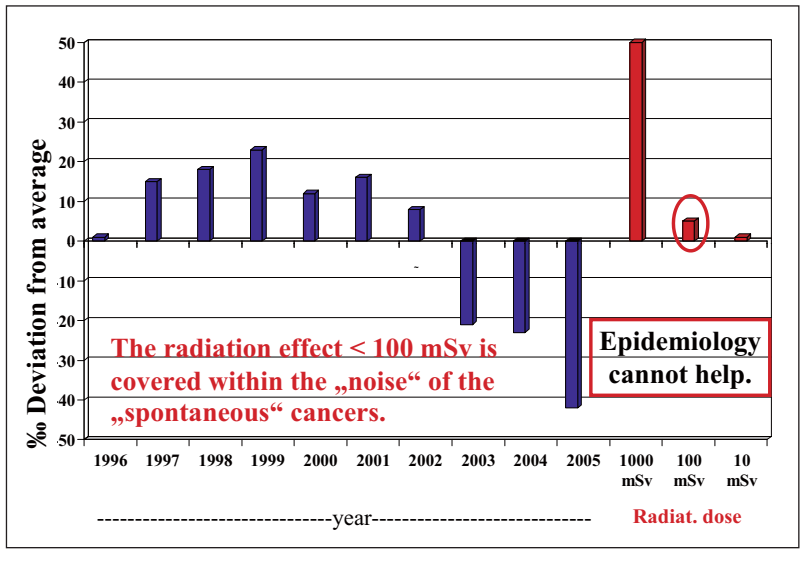

Fig. 2: Deviation of cancer mort. from the average (‰) in 1996–2005 (SEER-U.S.A.) and radiation effect (ICRP)

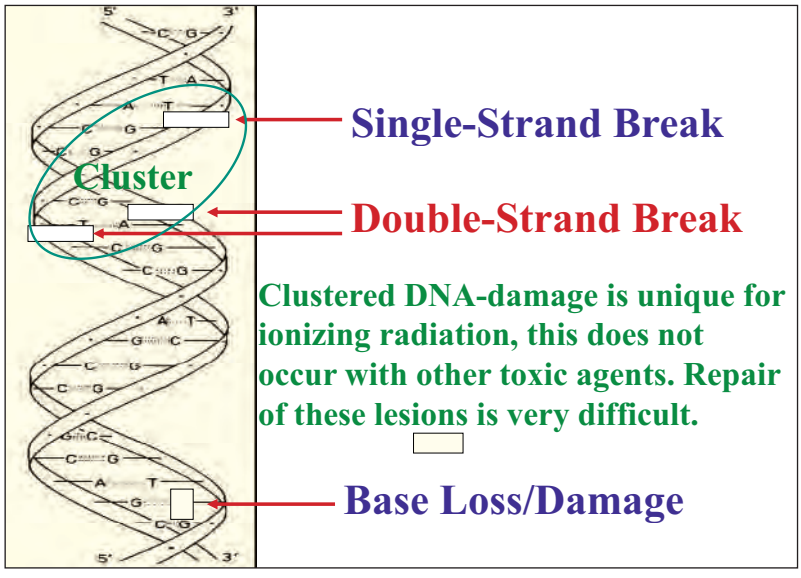

Fig. 3: Radiation damage to DNA (initiation for cancer)

tal evidence for this assumption. Intensive studies have been undertaken to evaluate the DNA damage. The prominent changes after exposure to ioinizing radiation are:

- Breaks of the polynucleotide strands, there can occur single strand breaks (SSB) or double strand breaks (DSB) (Fig. 3),
- Base damage, either a DNA base is completely lost or a base is radiochemically altered (Fig. 3) [2].

Analyzes of the track structure and of the distribution of ionisation events in the DNA helices revealed that clusters of damage occur after exposure to ionizing radiation: Very frequently damaging events occur in the direct neighbourhood to an SSB or DSB therefore and form a "complex SSB" or a "complex DSB" (Fig. 3). Since forty to fifty years it is known that these DNA damages can be repaired in living cells by different, very sophisticated enzymatic pathways. The complex regulation and the efficiency of these processes are dependent on the type of the DNA damage. In general the DNA repair of DSB and especially of complex DSB is slower and more difficult than that of other damage types. With DSB also misrepair can occur. Misrepaired DSB may be involved in the initial steps for the development of cancer.

With DSB also misrepair can occur

These mechanisms are not fully understood until now. Until about fifty years ago it was assumed that DNA is a stable molecule in order to maintain a healthy organism throughout lifetime. It was a firm dogma that any damage in the DNA is an irreversible process which leads either to a mutation or to cell death. Today it is well-known and proven that DNA is quite a labile molecule and the stability of the genome of the organism can be maintained throughout lifetime only by DNA repair. These processes are an essential part of evolution in nature. The occurrence of clustered DNA damage is unique for ionizing radiation [2, 16]. Chemical toxic agents generally cannot generate such clustered complex DNA damage in the low dose range. The damaging events of such agents are usually isolated events in the low dose range. Further the quantitative distribution of the various damage types is dependent on the radiation quality. Low LET radiation induces less DSB and especially less complex DSB than high LET radiation (Table 1). This is apparently the reason for the general observation that DNA damage of high LET radiation is repaired slower and less efficient than damage of low LET radiation and therefore high LET radiation leads to higher radiation effects than low LET radiation when equal absorbed doses are compared. Fig. 4 shows DNA damage in human cancer cells after irradiation with 2 Gy X-rays and 1 Gy neutrons (6 MeV) (100 percent at time zero) at different times of incubation for DNA repair thereafter [4].

In all living mammalian cells DNA is associated with proteins mainly histones in order to form chromatin. After radiation exposure several DNA damage associated histone modifications have been described. Thus the histone H2AX becomes phosphorylated locally to the DNA damage and appears as -H2AX which is recognized by antibodies so that the spots with the DNA damage can be made visible with immunofluorescence microscopy. By this technique DSB can be recognized and counted in a very sensitive manner. Thus it has been shown that DSB can be observed after low LET radiation doses of several mSv [17]. Further it has been shown that the efficiency of DNA repair is dependent on the genetic disposition. The radiosensitivity of individuals can differ widely due to the genetic disposition (Fig. 5). Most humans fall with respect to their radiosensitivity into a certain range with a Gaussian distribution. However, some

DNA-Dam. (%)	100 keV Electrons	2 MeV α-Particle
Bas.-Damag.	81.8	53.3
SSB	16,9	23,1
Compl. SSB	0,71	8,70
DSB	0,47	4,01
Compl.DSB	0,12	11,0
SSB/DSB	30	2

Table 1: DNA-damage after exposure to ionizing radiation; modified from [2, 4]

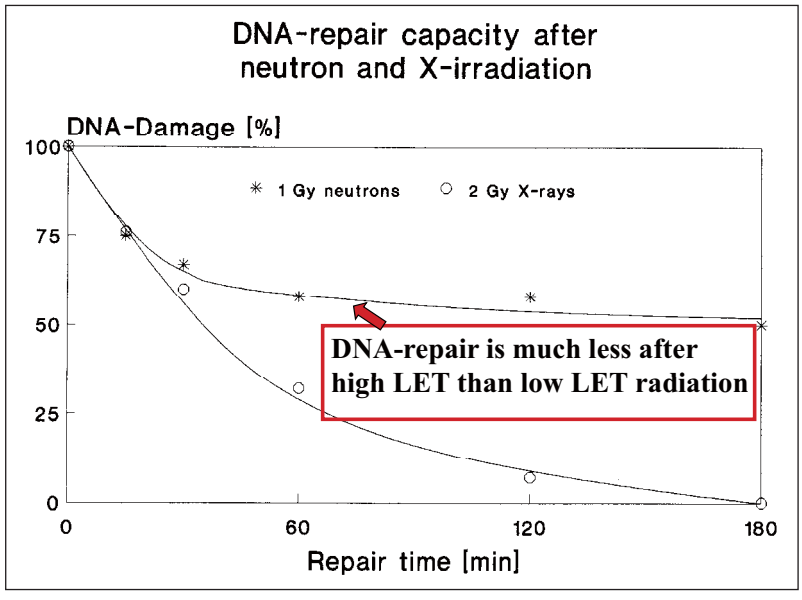

Fig. 4: Permanent tumor cell cancer MeWo

individuals have been observed with a very strong increase of radiosensitivity by cellular studies and clinical observations. These persons show a strong repair deficiency (Fig. 5; AT-patient and patient with "strong side effects") [4, 18, 19]. With these individuals all deleterious radiation effects are enhanced.

Dose modifying phenomena

Extensive biological studies have demonstrated during recent years that several biological phenomena ("New Biology") can modulate the dose response in the low dose range. These phenomena may also modify the dose response curve in various ways in the dose ranges where no significant epidemiological data on cancer induction are available (Fig. 6). Very important phenomena are DNA-repair processes which have already been discussed. Further adaptive response, apoptosis, bystander effects, genetic disposition, genomic instability, hyperradiosensitivity and immune response have to be mentioned. Some of these phenomena will be discussed in the following.

Adaptive response

Adaptive response has been frequently observed during the last 20 years with many organisms starting with bacteria up to mammalian organisms including humans [20]. In general biological objects, usually cells like bacteria or human lymphocytes, are irradiated with a low radiation dose (adapting dose in the range of 5 to 200 mGy), about 4 to 24 hours later a higher dose (challenging dose in the range of 1 to several Gy) is given and then the biological effects (with lymphocytes usually chromosome aberrations) are measured. In parallel the effect of the challenging dose only is measured. Quite often the radiation effect is reduced with the combination of adapting dose plus challenging dose in comparison to the effect of the challenging dose alone (Fig. 7). The cells have become more resistant against ioinizing radiation within the interval, they are adapted. Apparently the DNA repair has become more efficient by adaptation [20, 21]. Such effects have been shown in many cases throughout the whole animated nature with prokaryotic as well as eukaryotic organisms.

However, the effects can be very different between individuals (Fig. 7). The red columns represent the data in peripheral lymphocytes from a person with a strong adaptive response whereas the adaptation is very low and not significant with the second person (green columns). The adaptive response is apparently dependent on the genetic disposition. No adaptive response was observed in cells from individuals with hyperradiosensitive syndromes like Ataxia telangiectesia (AT). Several studies have shown that no or very little adaptive response developed with high LET radiation. During prenatal develop-

DNA-repair processes very important phenomena

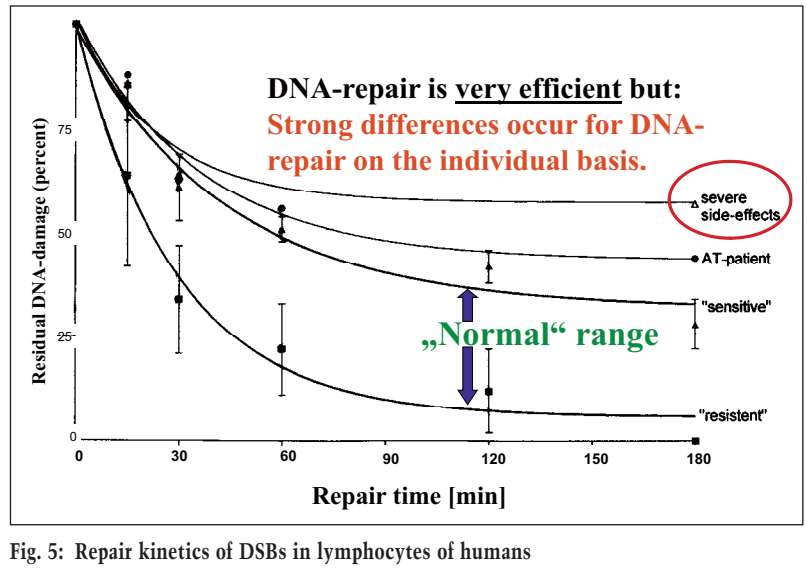

Fig. 5: Repair kinetics of DSBs in lymphocytes of humans

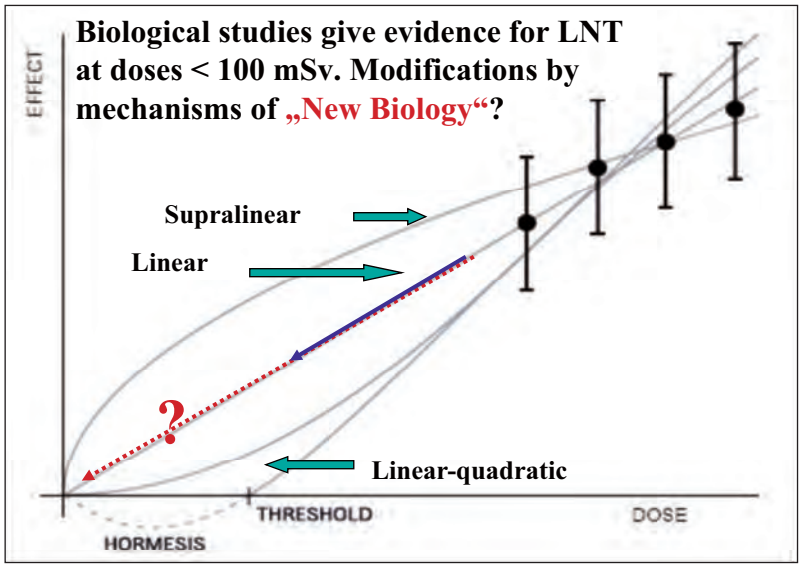

Fig. 6: Possibilities of extrapolation into the lower dose range

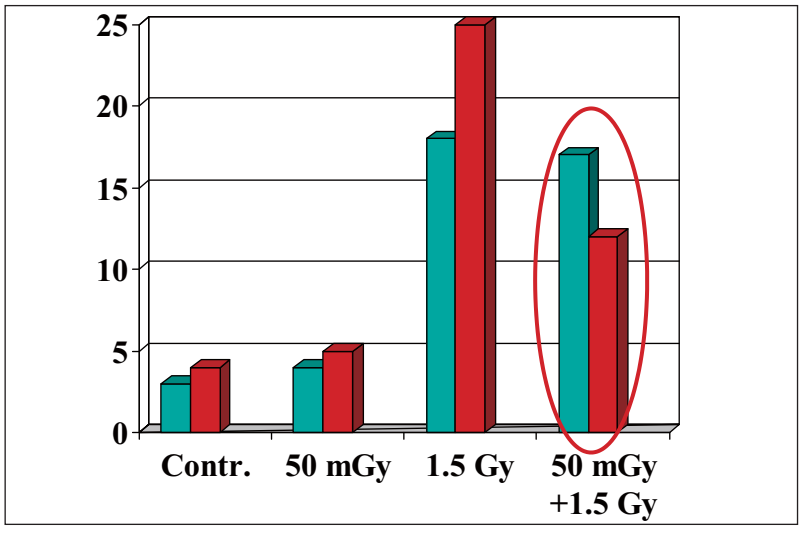

Fig. 7: Adaptive response in lymphocytes of two human donors (Adapt. D: 50 mGy; Chall. D: 1.5 Gy)

ment no or little adaptive response could be observed and further it has been found that adaptive response decreases apparently with age. It has also to be considered that very distinctive conditions with respect to the seize of the adapting dose and its dose rate, the time interval between adapting and challenging dose and other parameters have to be kept within certain limits in order to observe adaptive response [21]. Thus it can be concluded that adaptive response is a very important biological phenomenon of high scientific interest. However, it has a number of limitations, it is not an universal phenomenon, it does not operate in generality under all conditions.

Apoptosis

Apoptosis is a very powerful cellular mechanism to eliminate damaged or no longer needed cells e.g. during prenatal development by triggered intracellular processes. It can be increased after radiation exposure and it is assumed that apoptosis may also eliminate malignant cells so that the cancer risk is reduced. It has further been shown that small radiation doses can induce an adaptation to increased apoptotic activities but again this differs very much between individuals [21]. Apoptotic cell death is induced by complex intracellular signal transduction mechanisms which is triggered and regulated by a number of molecular factors (e.g. the tumour suppressor p53). These factors are also connected sometimes to the cycle of cell proliferation. At these branching points the cell can decide to undergo apoptotic cell death or proliferation (Fig. 8). In many cancers the tumour suppressor p53 or other regulating factors are inactivated by mutation or other translational processes. In these cells apoptosis is reduced and

Apoptosis a very powerful cellular mechanism

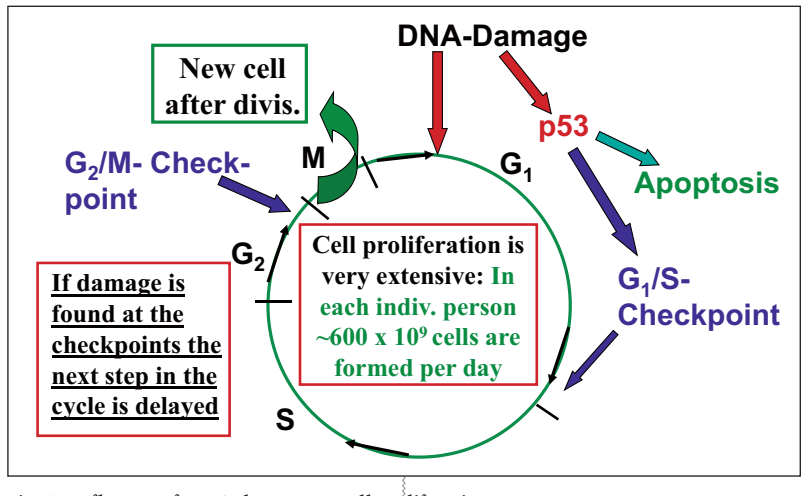

Fig. 8: Influence of DNA-damage on cell proliferation

Developm. Stage (Division of Blastom.)	CA per 100 Metaph.	
	without	with X-R.
1-Cell → 2-Cell	2.3	20.1
2-Cell → 4-Cell	4.2	16.3
4-Cell → 8-Cell	7.7	18.6

Table 2: Chromosomal aberrations (CA) in preimplantation mouse embryos without and with X-ray exposure (1 Gy) 1 h p. c. [23]

thus also the mechanism of cell elimination by apoptosis does not work [7, 22]. Therefore apoptosis can certainly be a mechanism to reduce the development of cancer after radiation but there are a number of situations were this mechanism does not operate.

Radiation-induced chromosomal damage

For a long time it was accepted that the radiation-induced chromosomal damage is expressed at the first mitosis taking place after a radiation exposure. Nowadays it is well-known, however, that this is not the case but it has been clearly demonstrated that new chromosomal aberrations also appear at later mitotic cell divisions. For such experiments female mice were irradiated after conception when the conceptus was still in the zygote (1-cell) stage and chromosomal aberrations were measured during the following mitotic cell divisions (1-cell to 2-cell; 2-cell to 4-cell and 4-cell to 8-cell stage). It was surprising that a considerable number of chromosomal aberrations was observed not only in the 1st division but also in the 2nd and 3rd divisions (Table 2) [23]. It was even more surprising that an increased number of chromosomal aberrations was found in fibroblasts which were obtained from foetuses just before birth. This means that despite a normal foetus had developed from the irradiated zygote some radiation damage had developed and was expressed in the foetal cells many cell generations later around birth(Table 3). The cells had developed an increased "instability of the genome" [24]. Surprisingly the patterns of the chromosomal aberrations in the foetal cells which developed from the irradiated zygotes are the same as in foetal cells from unirradiated zygotes while the patterns are different in the first mitosis after radiation exposure [25]. Such effects have been found in many cell systems and organisms (in vivo and in vitro) during the last 20 years [2, 7, 26, 27, 28].

Small doses can induce genomic instability

Mouse Strain	Control	1 Gy
C 57 BL	2,8 %	21,7 %
HLG	7,3 %	12,0 %

Table 3: Chromos. aberrations (% of mitoses with aberr.) in fibroblasts of fetuses of mice (19 d p.c.) after X-irradiation of zygotes (1 h p. c.) [24]

Genomic instability

Besides cytogenetic effects genomic instability has also been observed for a number of other biological endpoints e.g. cell survival, cell transformation. It can also be transmitted to the next generation of mice [25]. Genomic instability develops after high and low LET radiation [27]. Not quite clear is the dose response, the lowest radiation doses are usually in the range of several hundredmGy X-rays after which significant effects for the increase of genomic instability could be measured [25]. However, Okada et al. [29] observed an increase of DSB measured with the immunofluorescence -H2AX method after more than 20 cell generations of a radiation exposure with 1 mGy carbon ions. This is the radiation dose averaged over all cells, however, only one in 18 cells is exposed under these conditions. Thus the dose in the exposed cell is around a factor of

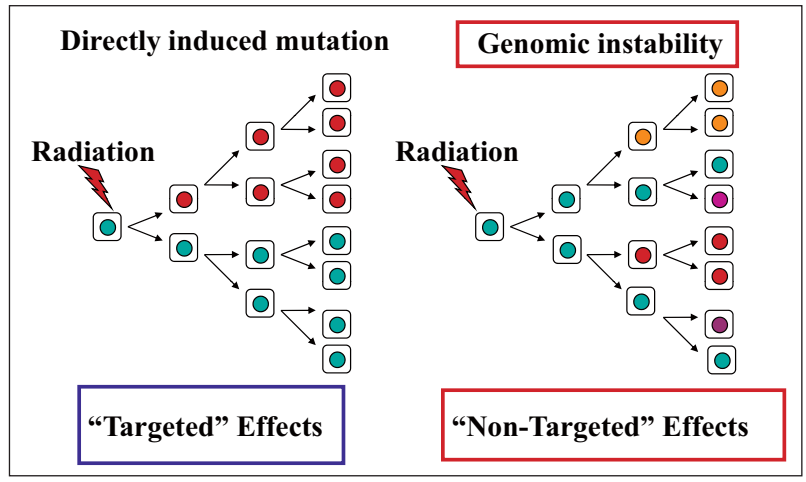

Fig. 9: Radiation-induced genomic instability as a new mechanism of mutagenesis

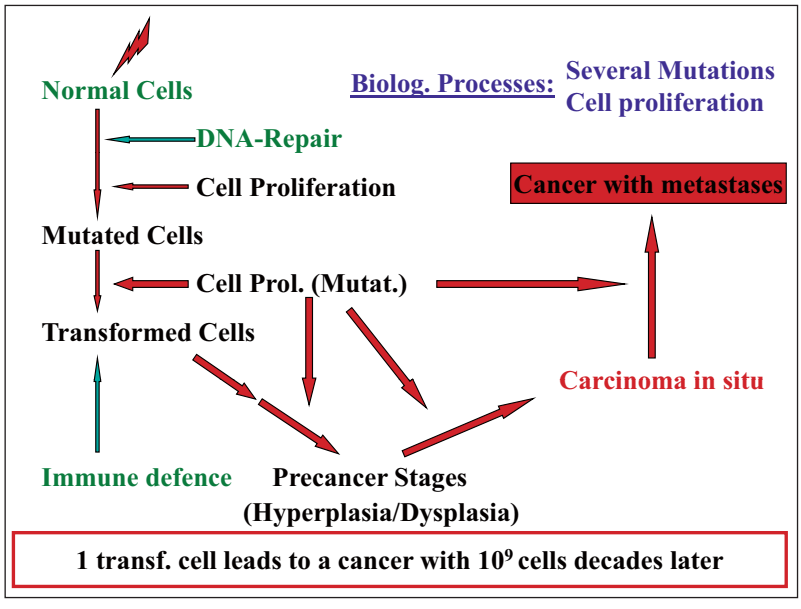

Fig. 10: Mechanism of cancer development

twenty higher. Nevertheless these data show that possibly small doses can induce genomic instability. Under the conditions of radiation-induced genomic instability the chromosomal damage is not seen in the cell which has been irradiated but in descendent cells many cell generationslater which have not been exposed to radiation. These effect are epigenetic in nature and the term "non-targeted" effect is used (Fig. 9).

Bystander effects

Besides these phenomena extensive experimental studies have been performed during last years on the so-called bystander effects. Thus it has been observed in cell cultures with single cell irradiation that not only the exposed cells show a response but also unexposed neighbour cells [26, 27, 28]. These bystander effects have been mainly studied with cells in vitro. They may lead to an enhancement of the radiation effects in vivo. However, also protective effects have been discussed in this connection. Nevertheless all these phenomena can have the ability to modify the dose response in the low dose range. In which way this could happen is unclear until now. It should further be stated that in the development of these radiation effects epigenetic effects are involved although the mechanisms for bystander effects and for the increase of genomic instability are not clear at all. These phenomena are intensively studied in large research projects (e. g. EU-project NOTE) in order to find its impact on the dose response in the low dose range and to formulate a "new paradigm" for radiological protection. The complexity of carcinogenesis is by far not understood until now a new approach, considerations of system biology may be helpful in this situation [30].

Nature has to be very efficient

Mechanism of carcinogenesis and association with genomic instability

The present concept about the mechanism of cancer development is roughly the following:

Cancer apparently affects the whole body

The initial events are changes/damage of DNA e.g. by ionizing radiation which may be repaired completely or the damaged cell starts to proliferate with either unrepaired or misrepaired DNA. In the latter case the daughter cells will carry a mutation, further proliferation can lead to cell transformation, malignant cells are formed. These cells may stay silent for many years, during which they can be removed by apoptosis or immune defence. However, also further mutations by radiation or facilitated by genomic instability may alter the regulation of cell proliferation which stimulate the whole process to result in pre-cancer stages. After further cell proliferation and mutations a carcinoma in situ is formed which then can

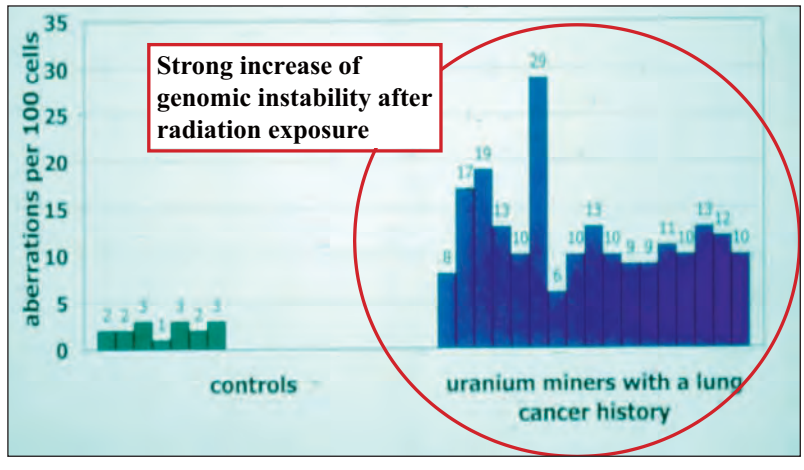

Fig. 11: Chromosome aberrations in peripheral lymphocytes of uranium miners with a lung cancer and of unexposed control persons

develop to cancer with metastases. Thus in summary the development of cancer is mainly accomplished by several successive mutations and extensive cell proliferation (Fig. 10). It is assumed that a cancer develops from one malignant cell. A cancer diagnosed in the clinic has around one or several billion cells [31]. The latency period (time for the development of a cancer) for most leukaemia is in the range of 5 to 10 years and for most solid cancers in the range of decades of years.

The cycle of cell proliferation (Fig. 8) is very well regulated by cytokines, cytokinases and other factors. In some tissues or organ systems (bone marrow, epithelia, skin) the cell proliferation is very intensive, around 600 billion cells are formed in an adult per day. Nature has to be very efficient. For these proliferation processes about $36H10^{20}$ DNA bases have to be arranged in the correct sequence. It is therefore not surprising that mistakes will occur which should be repaired as comprehensively as possible. Checkpoints exist in the cell cycle before the cell starts DNA synthesis (S) or mitosis (M). In case of damaged DNA the further migration through the cycle can be stopped (G_1- or G_2-block) for a certain time (hours) at these checkpoints. The cell tries to repair the damage at these checkpoints before it continues in the cycle (Fig. 8). However, cells can arrest only for a certain time after that they will continue although some damage is still left. During the development of cancer changes or complete disruption of the regulatory processes occur in the cell cycle by mutations of regulating factors. One of the features of cancers is that cell proliferation never stops. In normal tissues and organs cell proliferation reaches through feedback mechanisms a steady state equilibrium. The renewal of cells is in agreement with the loss of cells. This is not the case for cancers. The mentioned regulatory mechanisms are disrupted. Further it is well-known that cancer cells have an increased genomic instability [31, 32]. However, it is interesting that the increased genomic instability is apparently not limited to the cancer cells but also occurs in normal cells like peripheral lymphocytes of the cancer patient. Thus an increased genomic instability was observed in lymphocytes of uranium miners who experienced radiation exposures in the mines decades ago and who had developed a lung cancer (Fig. 11) [33]. Cancer is apparently a disease which is not only localized to the tumour tissue itself but affects the whole body.

Clinical experience and experimental studies have shown that several syndromes with specific genetic predisposition for high radiosensitivity exist which have been described genetically with their molecular features: Ataxia telangiectasia, Bloom´s Syndrome, Fanconi Anemia, Li Fraumeni Syndrome, Neurofibromatosis and Retinoblastoma [18]. All individuals with these syndromes show proneness for cancer, reduced DNA-repair and/or regulatory changes of the cell cycle as well as increased genomic instability. These data demonstrate a strong evidence for a causal association between genomic instability and cancer. The length of telomeres may be important for the genomic instability. – Telomeres are nucleotide sequences which terminate and stabilize the chromosomes. – Studies with patients who were treated with radiation for the malignant disease M. Hodgkin showed a reduction in the length of telomeres in comparison to unirradiated control persons. The reduction of telomeres was most significant in those patients who developed a secondary cancer after treatment. In a group of patients who were followed prospectively after radiotherapy two patients developed a secondary cancer and again the telomeres were especially shortened in these patients (Table 4). In these patients also the chromosome aberrations were measured in lymphocytes and the number of chromosome aberrations was higher in those patients whose cells had reduced telomeres. A good association between the increase of genomic instability and reduction of the telomeres was seen (Table 4) [34].

Population	Number of Pat.	Telomere Len. (kb)	CAs per Cell
Healthy Donors	30	11.7	0.003
Prospect. HL-Patients	73	8.3[1,3)]	0.026[2)]
Sec. CA after HL-Pat. Tr.	28	6.6[2)]	0.164[2)]

[1)]p<0.001; [2)]p<0.0001; [3)]2 Pat. with Sec.CA: Telom. 6 and 7.5 kb

Table 4: Telomere length and chromos. aberrations in control persons and patients w. M. Hodgkin (HL); M. Karcher et al., 2007

Radiation-induced cancer depends on many factors

Conclusions

Radiobiological research has resulted in the discovery of some fundamental

general biological phenomena (e. g.): Induction of mutagenesis by an exogenous agent, discovery of DNA-Repair processes, discovery of the cell cycle for cell proliferation, induction of increased genomic instability by a toxic agent. It has made strong contributions to radiological protection.

Epidemiological studies are important in order to evaluate quantitative risk factors for cancer after radiation exposure, however, they will not solve the open question about the risk in the low dose range (<100 mSv). Biological studies show effects (e.g. DSB; chromosome aberrations) down to dose ranges of several to 50 mSv which is lower than with epidemiology (Fig. 6, blue and red arrows). These studies support the view that no threshold exists for certain effects like mutations. How much such effects contribute to the development of health effects has to be solved. Observations of radiation effects <1 mSv appear impossible due to background effects by endogenous processes and radiation effects from natural sources. Genomic instability is associated with the development of cancer. It is increased in all individuals who have a high radiosensitivity. Studies of „new biology"-processes modulate and interact with the development of late radiation health effects. They may lead to a modification of the LNT model but the impact and in which way cannot be foreseen in the moment. Unfortunately the biological radiation effects especially the late effects like cancer cannot be discriminated from the "spontaneous" effects.

Radiation-induced cancer is dependent on many factors. It differs from organ to organ according to organ-specific, regulatory biological processes. Therefore the dose response is different for various cancer entities etc. For a uniform system in the low dose range (both sexes, all ages, all sensitivities, all radiation qualities) LNT with reference values appears to be the only way to go for prospective radiological protection with the appropriate safety. In a number of cases this model certainly leads to overestimation of the risk but this should be accepted for today. The LNT risk model is not only used for ioinizing radiation but also for most genotoxic substances [4].

However, for individual risk evaluation individual factors (e.g. sex, age, exposure conditions, possible genetic predisposition) have to be used. The LNT model in connection with effective dose should not be used for such purposes. In the low dose range the uncertainties of dose estimates and risk evaluation are high and should be considered. The radiation exposures from natural sources and other background risks e. g. of cancer interfere with the risk evaluation. Collective dose usually based on low individual doses is not useful for risk evaluation. It is a valuable tool for optimisation in radiological protection [6].

Open questions for biological research in the low dose range

Can the measurements in the low dose range be improved? What are the mechanisms and impact of these data for health effects?

When do the first malignant cells appear for the development of a cancer? Is one malignant cell enough for the development of this health risk?

What is the impact of the phenomena of „New Biology" on the shape of the dose effect relation in the low dose range?

Is there still a possibility to find a „Specific Signature" for radiation-induced health effects? ■

KEYWORDS/STICHWORTE

Cancer Induction, Cellular Reactions to Radiation, Radiation Effects, Radiological Protection
Carzinogenese, Strahlenschutz, Strahlenwirkung, Zellreaktionen bei Strahlenexposition

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