Chapter 2
Disturbance of Hereditary Material Reserves Is the Main Instrument of Stress

Abstract This review presents data on the low-dose radiation effects and their mathematical models. Its purpose is to demonstrate that radiation stress leads to processes of instability that can be revealed as different phenomena. The phenomena of radioadaptation, nonlinear response induced by low-dose irradiation, hormetic effect, and continued instability across generations, and stimulation of proliferation are considered. Our special interest is the investigation of the bystander effect which clarified some of these phenomena. The regularities of the bystander effect, genomic and transgenerational instability are considered. The modelling of these radiation effects is discussed: the models offered by Yu.G. Kapultsevich (probabilistic), D.J. Brenner et al. ("Bystander and Direct"), H. Nikjoo and I.K. Khvostunov (Diffusion model), and B.E. Leonard ("Microdose Model") are presented. The investigations of Russian scientists and the Timofeeff-Ressovsky school are presented as being of special interest to Western scientists owing to this information not having been published in the West due to the cold war.

Keywords Low-dose irradiation • Radioadaptation • Nonlinear response • Hormetic effect • Stimulation of proliferation • Bystander effect • Genomic instability • Transgenerational instability • Probabilistic model • Bystander and Direct model • Diffusion model • Microdose Model

2.1 Preamble

In 1939 N.W. Timofeeff-Ressovsky published the fundamental ideas of the microevolution process (Timofeeff-Ressovsky 1939). He considered dramatic fluctuations of genotype material in populations leading to the high mortality of organisms as essential equipment for evolution because a new genotype can only be multiplicated at low concentrations of the existing ones.

Such a situation is realized by a stress factor: its mechanisms rapidly increase the number of new mutations in the population coupled with a strong selection of

V.L. Korogodina et al., *Radiation-Induced Processes of Adaptation: Research by statistical modelling*, DOI 10.1007/978-94-007-6630-3_2,

the fitted genotype. The regularities of the stress response are the same for any live system, although the details can alter at different levels of life organization. This chapter considers the disturbance of hereditary material reserves[1] by stress as its main instrument, and some principles of adaptation will be demonstrated.

2.2 Low-Dose-Radiation Effects

2.2.1 Some Regularities of Adaptation in Pre-molecular Investigations

History of the investigations of low-dose-radiation effects: In the mid-1950s, investigations of low-radiation biological effects were organized in the USSR at the South Urals laboratory by Nikolay W. Timofeeff-Ressovsky (Timofeeff-Ressovsky and Tyuryukanov 2006; Timofeeff-Ressovsky and Timofeeff-Ressovskaya 2006). N.W. Timofeeff-Ressovsky and his laboratory researchers N.V. Luchnik, N.A. Poryadkova, E.I. Preobrazhenskaya, and others described a nonlinear dependence of cytogenetic effects on the radiation dose (Timofeeff-Ressovsky et al. 1950–1954; Timofeeff-Ressovsky 1956; Luchnik 1958) (the proportional dependence of mutation frequency on dose irradiation had been established earlier (Timofeeff-Ressovsky et al. 1935)). This was the first biological description of the non-linear effects induced by the low-radiation factor. From the 1960s on, the research by N.W. Timofeeff-Ressovsky and his colleagues was continued at the Russian Institute for Medical Radiology in Obninsk where the famous Timofeeff-Resovsky radiobiological school was established (Korogodin 1993).

The phenomenon of radioadaptation: In the mid-twentieth century, anthropogenic radioactive contamination of territories became a significant factor in ecology, and adaptation of natural populations to irradiation was systematically studied. In the USSR these investigations were mainly performed at the Russian Institute of Agricultural Radiology and Agroecology (Obninsk) and the N.I. Vavilov Institute of General Genetics (Moscow). The scientists of these institutes studied the influence of an artificially high radiation background on the natural plant populations (Cherezhanova and Alexakhin 1971) in the zone of the Kyshtym and Chernobyl accidents (Shevchenko et al. 1999).

The analysis of the consequences of the Kyshtym radiation accident in the South Urals (1957) showed a high variability of cytomorphological and physiological characteristics in plants (reviewed in (Pozolotina 1996)). The scientists described the plant radioresistance increasing under chronic irradiation. This phenomenon was called “radioadaptation”. V.A. Shevchenko suggested that the population divergence

[1] Here we consider the changes of cells and chromosomes.

on radiation resistance was related to changes in the repair system efficiency (Shevchenko et al. 1999).

These results agree with the increased mutation frequency in barn swallows (Ellegren et al. 1997) and in wheat upon chronic exposure to the ionizing radiation produced by the Chernobyl accident (Kovalchuk et al. 2000, 2003).

The nonlinear response induced by low-dose irradiation: In the mid-1990s, E.B. Burlakova published the results of the experiments in Russian journals, which showed the following: the low-dose-radiation effect has a non-monotonic character; there is an inverse relation of the low-dose effect on radiation intensity; the response depends on the initial characteristics of biological objects; low-dose-rate radiation is more effective than acute in some intervals (Burlakova 1994; Burlakova et al. 1996, 1999, 2000). The hypothesis suggested that the repair systems induced by low-dose radiation differed from those that worked at sub-lethal doses (Burlakova 1994). Natural investigations have shown increased radiation efficiency in populations polluted due to the Chernobyl (Geras'kin et al. 1998) and Kyshtym (Shevchenko et al. 1992) accidents.

Both hypersensitivity and radioresistance was also demonstrated on mammalian cells that were explained by the hypothesis of inducible repair systems (overviewed in (Averbeck 2010)). It was shown that stress factors activate repair systems, the operation of which results in an accumulation of abnormalities (Longerich et al. 1995).

At present, the nonlinear effects are considered to be the result of the bystander effects and genomic instability coupled with the stress-induced specific repair systems (Mothersill and Seymour 2005; Averbeck 2010). Although the nonlinear dose-effect is described for different objects, it remains discussible (Zyuzikov et al. 2011; Little 2010). One of the debatable questions is a linear no-threshold concept linked with the problem of radiation risks assessment (Vaiserman et al. 2010).

Hormetic effect: In the 1970s, data were published on the stimulation effect of low-dose radiation. The so-called radiation-induced hormetic effects were discovered in many branches of life sciences (Luckey 1980; Kuzin 1993; Petin et al. 2003) including protection against spontaneous genomic damage (Feinendegen 2005). This phenomenon can be explained by different reasons.

Hormesis induced by low-dose ionizing radiation often reflects stimulation of cell proliferation (Gudkov 1985; Liang et al. 2011).

It was found that low-dose radiation induces an "adaptive response", which implies a pre-treatment of cells with a low-radiation dose followed several hours later by exposure to a much higher dose (Upton 2001). The adaptive response can reduce radiation-induced DNA damage, mutagenesis, and the frequency of chromosomal aberrations, micronuclei and cell transformants. In (Rigaud and Moustacchi 1996), the authors reviewed the experimental results showing that a prior exposure to a low dose of ionizing radiation induces an adaptive response expressed as a reduction of mutation in various cell systems. The published review (Mothersill and Seymour 2004) considers how bystander effects may be related to observed adaptive responses. In the authors' opinion, it is possible that low-dose

exposures cause removal of cells carrying potentially problematic lesions, prior to radiation exposure. Then, the adverse, adaptive or apparently beneficial response will be related to the background damage carried by the original cell population.

Continued instability across generations: As early as 1925, G.A. Nadson and G.S. Filippov (1925) described the mutagenic action of radium on mold, fungi and yeasts. Shortly thereafter, these authors reported the "*en masse*" appearance of morphologically-diverse colonies and cells in the progeny of irradiated yeasts (Nadson and Filippov 1932). These studies were stopped in the USSR after Filippov's death from tuberculosis in 1934 and Nadson's arrest (1937) and execution in 1939. In France, studies of this kind were started by Lacassagne and co-authors (1939), but were terminated due to World War II.

At the end of the 1960s, V.I. Korogodin and his colleagues studied the so-called "cascade mutagenesis" that is a continuous (several hundreds of cell generations) appearance of new races (phenotypic variants) in individual unstable clones formed with high frequency in diploid yeasts after ionizing radiation or any other mutagenic treatment (Korogodin and Bliznik 1972). It was shown that cascade mutagenesis was induced by primary sub-lethal lesions. The phenomenon is that the mutation process, caused by a single irradiation act, occurs at a greater rate, much more than 10^{-2} mutations per cell per division. In diploid cells, the effects of several primary lesions may be summarized and inherited resulting in various mitotic disorders (Korogodin et al. 1977). It was also shown that 60 % of new races were originated in the shoulder region of the survival curve (Korogodin et al. 1972), and their number increased under non-optimal conditions of cultivation (Bliznik et al. 1974). From 1972 to 1977, Korogodin and his colleagues showed the relation of this phenomenon to chromosomal instability (a series of articles published in the Russian journal "Radiobiologiya", Vs. 12–17).

Proliferation: It was shown on human lymphocytes that cells at different stages of the cell cycle differ in sensitivity (Boei et al. 1996). Thus, the cellular population consists of proliferated radiosensitive and radioresistant subpopulations, and resistant resting cells. The heterogeneity of cells results in their different proliferative activity (Gudkov 1985) and plays an important role in the preservation of a proliferated cell pool.

The low-dose radiation activates division within the resting cells. For the first time, Nikolay V. Luchnik published data on the stimulation of resting cells leading to proliferation in plants (1958). He noticed that this mechanism was not compensatory with respect to the cells' killing, but independent.

2.2.2 Bystander Effect

History: A bystander effect was described by W.B. Parsons et al. (1954), who studied factors which induced chromosomal damages (clustogenic factors) registering in the blood of irradiated patients as far back as 1954. By the description of the

authors, the bystander effect was observed in the cells, which were non-irradiated but still behaved the same as the irradiated ones: they died or demonstrated genomic instability. In 1968, the data of such effects were described by other scientists (Goh and Sumner 1968). In 1997, the hypothesis was offered by C.B. Seymour and C. Mothersill that the signal (or factor) produced in a medium by an irradiated cell was able to induce genomic instability-type effects in a distant progeny (Seymour and Mothersill 1997). At present, the bystander effect induction is well-documented at the low dose of soft and dense radiation (Little et al. 1997; Schettino et al. 2003), both *in vitro* (Morgan 2003a) and *in vivo* (Morgan 2003b).

The standard paradigm of the radiation biological effect ("target theory") lies in the fact that biologically-meaningful consequences of that effect are connected with DNA damage (Timofeeff-Ressovsky and Zimmer 1947). Particularly, double strand breaks of DNA are the reason for mutations, transformation of cells and their death (Pfeiffer 1998). In the 1990s, many reports on "non-targeted" effects were published. But these effects were not the result of the direct radiation effect for DNA. The authors observed abnormalities (chromatid exchanges (Nagasawa and Little 1992; Little 2000), chromosomal aberrations (Little 2000; Lorimore and Wright 2003), apoptosis (Mothersill and Seymour 1997, 2000), formation of the micronuclei (Prise et al. 1998; Sedelnikova et al. 2007), cells' transformation (Sigg et al. 1997), mutations (Zhou et al. 2000) and the gene expression changes (Hickman et al. 1994; Mothersill and Seymour 2001)) in non-irradiated cells, which were neighbors of the irradiated ones.

The bystander effect was manifested through the use of several different methods: studies of the effect were performed *in vitro* by a microbeam at the Cancer Institute (UK), when the fixed separate cells were damaged (Sawant et al. 2001; Belyakov et al. 2002); in another instance, while transferring the non-irradiated cells into the media where irradiated cells were cultivated, the effects were registered among the non-irradiated cells (Mothersill and Seymour 1997, 1998; Nagar et al. 2003); and it was also shown to occur by means of the probability approach which is based on irradiation of the cells' culture at the minute particle flux (Nagasawa and Little 1992; Deshpande et al. 1996). The main investigations were devoted to the death of cells, mutations and chromosomal aberrations (Mothersill and Seymour 2001). The bystander effect phenomenology was developed and published in (Mothersill and Seymour 2001; Morgan 2003a, b; Little and Morgan 2003; Lorimore and Wright 2003; Lorimore et al. 2003).

Dependence on the dose and dose-rate radiation: The authors (Schettino et al. 2003) studied the bystander effect induced by ultra-soft X-rays in V79 cells. The linear-square law of the cell survival dependence on dose irradiation and hypersensitivity were observed at low-dose radiation. The analysis of the distance between the non-irradiated damaged cells and non-damaged cells showed the clusters of bystander-damaged cells.

The bystander effect depends non-linearly on the dose irradiation (Hickman et al. 1994; Deshpande et al. 1996; Prise 2006), and its manifestation is maximal at low doses (Belyakov et al. 2000). Some authors assume that induction of the bystander effect has a threshold (Schettino et al. 2005; Liu et al. 2006).

Signaling: ***induction, transference and reception***: It is shown that irradiated mammalian cells can generate and transmit signals to the non-irradiated neighbors involving reactive oxygen species and nitric oxide species (Shao et al. 2006, 2008; Kashino et al. 2007; Portess et al. 2007). There are different data concerning the repair-deficient influence on the bystander responses (Mothersill et al. 2004; Nagasawa et al. 2003).

C. Mothersill and C.B. Seymour assume that small proteins and peptides can be signaling carriers from the irradiated cell to the non-irradiated one (2001); in some cases, direct cell contact is needed, and in others, it is not (Mothersill and Seymour 2002). It was shown that reactive oxygen species, such as superoxide and hydrogen peroxide, and calcium signaling are important modulators of bystander responses (Lyng et al. 2006).

2.2.3 Genomic Instability

Studies of the bystander effects showed their involvement in the demonstration of genomic instability. Genomic instability is characterized by increased changes in the genome, and manifests itself as chromosomal aberrations, genetic mutations and amplifications, late cell death, aneuploidy induction of micronuclei, and microsatellite instability (Watson et al. 2000; Little 2000; Mothersill and Seymour 2001; Little and Morgan 2003; Lorimore and Wright 2003; Lorimore et al. 2003; Kovalchuk and Baulch 2008; Averbeck 2010). Radiation induces genomic instability in the irradiated cell at delayed times after irradiation and in the progeny of the irradiated cell (Little 2000). Such instability may be a prerequisite for cancer. Genomic instability was observed *in vitro* (Morgan 2003a, 2011) and *in vivo* (Watson et al. 2000; Morgan 2003b, 2011).

Genomic instability was documented in blood samples from accidentally irradiated individuals, individuals after radiotherapy, survivors of Hiroshima and Nagasaki in 1977, liquidators and children of Chernobyl, human blood samples irradiated *in vitro*, and patients with cancer predisposition syndromes (Bloom's syndrome, Fanconi's anemia, Xeroderma pigmentosum) (Emerit et al. 1997).

The role of the dose and radiation quality: Genomic instability was observed both at high and low linear energy transfer (LET) (Aypar et al. 2011). But investigations have shown the LET-dependent induction and expression of genomic instabilities (Okada et al. 2007; Aypar et al. 2011).

To investigate the long-term biological effect of extreme low-dose ionizing radiation, the authors (Okada et al. 2007) irradiated normal human fibroblasts with carbon ions and gamma-rays. These studies have indicated that high-LET radiation (carbon ions) causes the effects which differ from those induced by low-LET radiation (gamma-rays), and that a single low dose of heavy ion irradiation can affect the stability of the genome of many generations after exposure. The experimental results published in (Kadhim et al. 2006) assume that the dose might

be the most significant factor in determining induction of genomic instability after low-LET radiation. In (Aypar et al. 2011) the authors have tested the hypothesis that irradiation induces epigenetic aberrations, which could eventually lead to genomic instability, and that the epigenetic aberrations induced by low-LET radiation differ from those induced by high-LET irradiations.

The authors (de Toledo et al. 2011) emphasize that the radiation dose and radiation quality (LET) are very important in determining the nature of the induced effect. Radiation type, dose rate, genetic susceptibility, cellular redox environment, stage of cell growth, level of biological organization and environmental parameters are the factors which modulate interactions among signaling processes and determine short- and long-term outcomes of low-dose exposures.

2.2.4 Transgenerational Response

History: Enhanced genetic changes continuing in descendants were observed and investigated by G.A. Nadson, B. McClintock, and C. Auerbach many years ago (Nadson and Filippov 1932; McClintock 1938; Auerbach and Kilbey 1971). These famous scientists considered radiation as an inductor of genomic instability (Nadson and Filippov 1925, 1932; Auerbach and Kilbey 1971; McClintock 1984). C. Auerbach obtained evidence of an increased mutation rate in the first-generation (F1) Drosophyla offspring of exposed its parents (Auerbach and Kilbey 1971). In the 1970s V.I. Korogodin and his colleagues investigated regularities of "cascade mutagenesis" on yeasts, when appearance of new races (phenotypic variants) continued in several hundreds of cell generations (Korogodin et al. 1977). Luning et al. investigated the frequency of dominant lethal mutations in the germline of non-exposed offspring of irradiated male mice, and obtained evidence for transgenerational destabilization of the genome (Luning et al. 1976).

Transgenerational instability: In recent years, evidence has been obtained for the induction of persistent elevated levels of mutation rates in the progeny of irradiated cells both *in vivo* (Morgan 2003a) and *in vitro* (Morgan 2003b). Dubrova et al. (2000) showed elevated minisatellite mutation rates in the mouse germline by low-dose chronic ionizing irradiation, and a potential contribution of genomic instability to transgenerational carcinogenesis has been assumed (Dubrova 2003).

Many authors have reported that the offspring of irradiated parents demonstrate transgenerational instability, and the number of affected offspring may substantially exceed the one predicted by the target theory (Luning et al. 1976; Wiley et al. 1997; Barber et al. 2006). The long-term destabilization of the genome could also lead to cancer. In (Vorobtsova et al. 1993), the incidence of cancer in the offspring of irradiated male mice painted with acetone or with acetone solution was analyzed. The authors showed an elevated incidence of cancer among the offspring of the irradiated males. The studies of genetic instability across generations of low-dose-rate

irradiated mice which indicated the genetic instability in the F1, F2, and F3 generations from the irradiated males were published in (Zaichkina et al. 2009).

Transgenerational response is an attribute of the genome-wide destabilization: Investigations performed by Yu.E. Dubrova, R.C. Barber and their colleagues have shown that the expanded simple tandem repeat (ESTR) mutation rate in DNA samples extracted from the germline (sperm) and somatic tissues taken from the F1 offspring of male mice, exposed to 1 or 2 Gy of acute X-rays, are equally elevated in both cases (Barber et al. 2006). Transgenerational changes in somatic mutation rates were observed by studying the frequency of chromosomal aberrations (Vorobtsova 2000), micronuclei (Fomenko et al. 2001) and lacI mutations (Luke et al. 1997) in the F1 offspring of irradiated male mice and rats. The referred data have demonstrated that exposure to ionizing radiation results in the induction of a transgenerational signal in the germline of exposed parents which can then destabilize the genomes of their offspring. Experimental studies on the transgenerational effects of post-Chernobyl paternal irradiation were performed and showed an elevated frequency of chromosomal aberrations among the children of exposed fathers (Aghajanyan et al. 2011).

Y.E. Dubrova (2012) analyzed the spectrum of delayed mutations resulting from the ongoing instability, and demonstrated the difference from those resulting from direct induction, which, at the same time, were very close to the spectrum of spontaneous mutations. This means that radiation-induced genomic instability may result from enhancement of the process of spontaneous mutation, and a genome-wide destabilization of the F1 genome could be attributed to replication stress.

Epigenetic changes and non-targeted radiation effects: The data published indicated that radiation-induced genomic instability, bystander, and transgenerational effects may be epigenetically mediated (Nagar et al. 2003; Kaup et al. 2006; Jirtle and Skinner 2007; Aypar et al. 2011). The epigenetic regulation of gene expression includes DNA methylation, histone modification, and RNA-associated silencing (Jaenisch and Bird 2003). Recent studies have demonstrated that ionizing radiation exposure changes epigenetic parameters in directly exposed tissues and in distant bystander tissues; transgenerational radiation effects were also proposed to be of an epigenetic nature (reviewed in (Kovalchuk and Baulch 2008)).

2.3 Modelling of the Radiation Effects

2.3.1 Probability Models

In 1935, N.W. Timofeeff-Ressovsky, K.G. Zimmer and M. Delbrük (Timofeeff-Ressovsky et al. 1935) published the paper “Über die Nature der Genmutation und der Genstruktur”, in which they described quantitatively the dependence of gene mutation frequency on the dose irradiation in Drosophila. The “hit principle”

and "target theory" were formulated in monographs by D.E. Lea (1946) and N.W. Timofeeff-Ressovsky and K.G. Zimmer (1947) in 1947–1948. The model postulated a single hit in a single target as a "triggering event" and explained the exponential form of the survival curve for single-hit events, i.e., the survival of irradiated viruses.

The sigmoid form of the curve "dose-effect" was investigated by Y.G. Kapultsevich and his colleagues (Kapultsevich and Petin 1977; Kapultsevich 1978). The Kapultsevich model postulates that the registered effect in cells is the result of a number of discrete damages caused by hitting in intracellular structures ("the targets"). The number of such damages is Poisson-distributed in cells. The authors studied the probability of cell division depending on the number of damaged targets. This probability model describes quantitatively the regularities of cell division in a wide interval of sub-lethal-dose irradiation (Kapultsevich 1978). This model doesn't consider the time-dependence of cell damaging.

2.3.2 Theoretical Models of Bystander Effects

Single-cell irradiators and new experimental assays are rapidly expanding the ability to detect a subtle biological phenomenon such as the bystander effect. Mathematical models are needed to interpret the results of the microbeam and low-dose experiments. Although there is increasing evidence that the bystander effects play an important role in the low-dose-radiation response, some models have been developed to account for these phenomena.

"Bystander and Direct" model: Brenner et al. (2001; Brenner and Sachs 2002) offered the so-called "Bystander and Direct" (BaD) model to explain the results of the α-particle microbeam experiments. The authors postulated a bimodal character of the bystander effect: "all" or "nothing" in the cells of a small bystander-hypersensitive subpopulation. The cells of this subpopulation are also sensitive to a direct hit of particles which inactivates cells. For α-particles the whole effect (Y) summarizes actions of the direct hit (D) and bystander effect (B): $Y = B + D$.

Cells that are directly damaged emit signals to the nearest cells that are not. The model doesn't consider the nature of the signal (k), which is the model parameter. Let us suggest that if the α-particle hits the cell, then any of the nearest hypersensitive k cells will be activated.

Non-hypersensitive cells can be activated only through a direct hit by the α-particle. Therefore, statistics of these events are a standard Poisson law. Its sample mean can be determined by a formula $D = \mu N$, where N is an averaged number of particles per cell nucleus, and μ is the other model parameter. Thereby, the model has two parameters.

These premises make it possible to describe satisfactorily the data presented in (Brenner et al. 2001). It is shown that an increase of exposure time at a constant irradiation dose leads to the inverse dose-rate-effect that is the increasing of the Y effect at the decreasing of the dose-rate-irradiation. The analysis has shown

that the bystander effect is observed only at low doses of ~0.2 cGy and less. At the lower doses, the bystander effect can dominate. If we are to extrapolate the risk from the sub-lethal dose interval where the direct hitting effects dominate, the underestimation of low-dose-radiation risk is possible.

Diffusion model: H. Nikjoo and I.K. Khvostunov (2004) developed a model of the radiation-induced bystander effect based on the diffusion principle of signal transferring. The Bystander Diffusion Model (BSDM) assumes that a low-molecular-weight protein can be emitted as the signal carrier from the damaged cell and diffuses in intercellular media to the undamaged cell. Cell inactivation and induced oncogenic transformation by the microbeam and broadbeam irradiation systems were considered. The model postulates that the bystander response observed in non-hit cells originates from specific signals received from inactivated cells. The bystander signals are assumed to be protein-like molecules spreading in the culture media by Brownian motion. The bystander signals are supposed to switch cells into a state of cell death (apoptotic/mitotic/necrotic) or induced oncogenic transformation modes. The model predictions for cell inactivation and induced oncogenic transformation frequencies closely correspond to the observed data from microbeam and broadbeam experiments.

The model can be used to explain the survival of cells studied in experiments on transferring the unirradiated cells into the irradiated cell cultural media. This model is also applicable to interpreting the dose-effect curve for survival and carcinogenic transformation of the cells irradiated by alpha-particles. In the case of irradiation with a constant fraction of cells, the transformation frequency for the bystander effect increases with the increase of the radiation dose. The BSDM predicts that the bystander effect cannot be interpreted solely as a low-dose-effect phenomenon. It is shown that the bystander component of the radiation response can increase with the dose and can be observed at high doses as well as low doses (Nikjoo and Khvostunov 2004). The validity of this conclusion is supported by the analysis of experimental results from the high-LET microbeam experiments.

A composite microdose adaptive response and bystander effect model: It is known that an adaptive response may reduce risks of adverse health effects due to ionizing radiation. But very low-dose bystander effects may impose dominant deleterious human risks. These conflicting effects contradict the linear no-threshold human risk model. The dose and dose-rate-dependent microdose model, which examines adaptive response behavior, was described by B.E. Leonard in (Leonard 2008a). The purpose of this work was to obtain new knowledge regarding adaptive response and bystander effects, and illustrate the use of the model for planning radiobiological experiments.

In (Leonard 2008a, b), the author published his work, which provides a composite, comprehensive Microdose Model (MM) that is also herein modified to include the bystander effect. The MM describes the biophysical composite adaptive response and bystander effects and quantifies the accumulation of hits (Poisson distributed, microdose specific energy depositions) to cell nucleus volumes. This model gives predictions of the dose response at very low-dose bystander effect

levels, higher-dose adaptive response levels and even higher-dose direct (linear-quadratic) damage radiation levels. The author found good fits of the model to both bystander effects data from the Columbia University microbeam facility and combined adaptive response and bystander effects data for low- and high-LET data.

The five features of major significance provided by the Microdose Model (Leonard 2008a) so far are: (1) single specific energy hits initiate adaptive response; (2) mammogram and diagnostic X-rays induce a protective bystander effect as well as adaptive response radioprotection; (3) for mammogram X-rays, the adaptive response protection is retained at high primary dose levels; (4) the dose range of the adaptive response protection depends on the value of the specific energy per hit; (5) alpha-particle-induced deleterious bystander damage is modulated by low-LET radiation.

2.4 Probability Approach to Risk Assessment of the Chromosomal Instability

Apparently the data mentioned above can be interpreted in different terms, including the "harmful" or "useful" aspects of the phenomena (Burlakova et al. 1996; Mothersill and Seymour 2005). It is useful to consider the influence of low-dose radiation in view of the nature law – adaptation (Korogodina et al. 2010). It is simple to analyze the adaptation processes using chromosomal instability, which could be an indicator of the bystander effect (Little et al. 1997; Lorimore et al. 2003).

The usual biological methods are based on averaged experimental values and give rough estimations of the chromosomal instability risks (Shevchenko et al. 1992). Contrarily, the risk assessments given by theoretical modelling are based on theoretical assumptions (Brenner et al. 2001; Brenner and Sachs 2002; Nikjoo and Khvostunov 2004; Leonard 2008a). The statistical view is based on the experimental data and allows one to consider resistant and sensitive fractions which follow different regularities. The structure of distributions of organisms on the number of abnormalities reflects the characteristics of the adaptation processes: the dose rate of the primary injuring, and intensities of the bystander processes and repair (Florko and Korogodina 2007; Korogodina et al. 2010). Statistical modelling can be used to investigate fundamental problems of microevolution processes and the risk assessment of genomic instability in ecology, epidemiology, medicine, and cosmic investigations.

2.5 Summary

The study of low-dose radiation effects began in the middle of the twentieth century. The Urals' N.W. Timofeeff-Ressovsky laboratory found the non-linear regularities (Timofeeff-Ressovsky et al. 1950–1954; Timofeeff-Ressovsky 1956; Luchnik

1958). Then, other low-radiation effects were investigated: hypersensitivity and elevation of radioresistance observed in radiation-polluted territories (Shevchenko et al. 1992), the stimulation of cells to divide (Luchnik 1958), the induction of adaptive response (Rigaud and Moustacchi 1996) and radiation hormesis (Luckey 1980) that protect cells against genomic damages, and instability across generations (Korogodin et al. 1977).

A new step in the investigations was established when the bystander effect was revealed.

Non-targeted effects: A bystander effect was described by W.B. Parsons et al. in 1954. In the 1990s, many reports of "non-targeted" effects were published. The authors observed abnormalities (chromatid exchanges, chromosomal aberrations, apoptosis, formation of the micronuclei, cells' transformation, mutations and gene expression changes) in non-irradiated cells, which were neighbors of the irradiated ones (reviewed in (Mothersill and Seymour 2001, 2006)). It was shown that the bystander effect depends non-linearly on the dose irradiation (Prise 2006). In 1997, the hypothesis was offered by C.B. Seymour and C. Mothersill that the signal (or factor) produced in a medium by an irradiated cell was able to induce genomic instability-type effects in a distant progeny (Seymour and Mothersill 1997).

The bystander effect is linked to the phenomenon of the radiation-induced genomic instability that manifests itself as chromosomal aberrations, genetic mutations, late cell death, and aneuploidy (Kovalchuk and Baulch 2008). The genomic instability was observed *in vivo* and *in vitro* (Morgan 2003a, b). Both non-targeted phenomena include intra- and intercellular signaling, involving reactive oxygen species (Averbeck 2010).

Transgenerational response: In recent years, evidence has been obtained for the induction of persistent elevated levels of mutation rates in the progeny of irradiated cells (Morgan 2003b). Dubrova et al. (2000) showed the elevated minisatellite mutation rates in the mouse germline induced by low-dose chronic ionizing irradiation. Experimental studies on the transgenerational effects of post-Chernobyl paternal irradiation were performed and showed the elevated frequency of chromosomal aberrations among the children of exposed fathers (Aghajanyan et al. 2011). These data have demonstrated that exposure of the individuals to ionizing radiation results in the induction of a transgenerational signal in the germline of exposed parents which can then destabilize the genomes of their offspring. The inheritable radiation-induced genomic instability in all F1 offspring is assumed to be an epigenetic type of transmission (Kovalchuk and Baulch 2008).

Modelling of the radiation effects: Some models were considered here. The first one was the probability model by Yu. G. Kapultsevich (1978). In this model, the experimental data were used. Such modelling helps to understand general regularities.

The theoretical models describe the processes based on the premises of scientists, and then the mathematical conclusions are compared with the experimental data. Such theoretical models were developed by D.J. Brenner ("BaD") (Brenner et al.

2001), B.E. Leonard (Microdose model) (Leonard 2008a, b), and H. Nikjoo and I.K. Khvostunov (Diffusion model) (2004). The mathematical modelling is aimed at studying some concrete problems.

Risk assessment: Statistical modelling is based on experimental data and allows one to study resistant and sensitive fractions (Florko and Korogodina 2007; Korogodina et al. 2010). It can be used to investigate the characteristics of microevolution processes and the risks of genomic instability in ecology, epidemiology, medicine, and cosmic investigations.

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http://www.springer.com/978-94-007-6630-3

Radiation-Induced Processes of Adaptation
Research by statistical modelling
Korogodina, V.L.; Florko, B.; Osipova, L.P.
2013, XVII, 183 p.,
ISBN: 978-94-007-6630-3