DIVISION OF RADIATION AND RADIOBIOLOGICAL RESEARCH

In 1998, the main directions of DRRR activity were concentraded on:

- radiation researches;
- radiobiological researches;
- radiation protection.

The first two directions were included in the Topical Plan for Scientific Research of JINR as a theme of first priority. Major tasks of the DRRR scientific programme in 1998 were:

– development of the experimental methods and radiation measuring techniques;
– development of the technique of radiobiological experiments and their carrying out by the charged particle beams;
– modelling of ionizing radiation interaction with matter and shielding calculations;
– radiation detector response study;
– radiobiological investigation of the regularities and the mechanisms of the mutagenic action of ionizing radiation with different LET on pro- and eukaryotic cells;
– investigation of biological effect of low doses of radiation with different LET and cells' recovery;
– development of the methods of target radiotherapy and diagnostics.

RADIATION RESEARCHES

Radiation investigations in 1998 were connected mainly with neutron detectors' study, the radiation environment prognostication at CyLab complex in Bratislava (Slovak Republic) and shielding calculations, physical support of the radiobiological experiments at JINR facilities.

The work for systematic study and optimization of parameters of neutron detector assemblies for the nuclear materials safeguards unattended radiation monitoring was prolonged. The prototype of neutron monitor on the basis of corona type gas filled counters, suitable for using in mixed fields with high dose rate gamma-radiation, was developed and tested.

The collaboration between DRRR and the Radiation Biophysics Lab of the US National Aeronautic and Space Administration (NASA) was continued. The system of monitoring instruments for physical support of radiobiological experiments at particle beams was designed. The second run of human peripheral blood lymphocytes irradiation was carried out at the LHE Synchrophasotron at the end of June 1998. The samples irradiated by the 1 GeV protons with absorbed doses 0.5-7.0 Gy, were tested at DRRR and mailed to NASA.

Radiation protection system design and shielding calculations of *CyLab cyclotron complex* were carried out.

Measurements of the double energy-angle distributions of the neutrons (in the energy range from thermal to several hundred MeV) emitted from thick targets irradiated with high-energy protons were continued [1]. The spectra and total neutron yields measurements were performed by the multisphere neutron spectrometer and activation detectors technique. The neutron spectra were unfolded by the statistical regularization method.

The *detectors responce study* was continued by the proton and carbon ion beams [2].

The code for prompt processing of activation detector data was developed.

Radiobiological investigations were performed on *mammalian cells in culture, human lymphocytes, haploid and diploid yeast, bacteria and plant cells.*

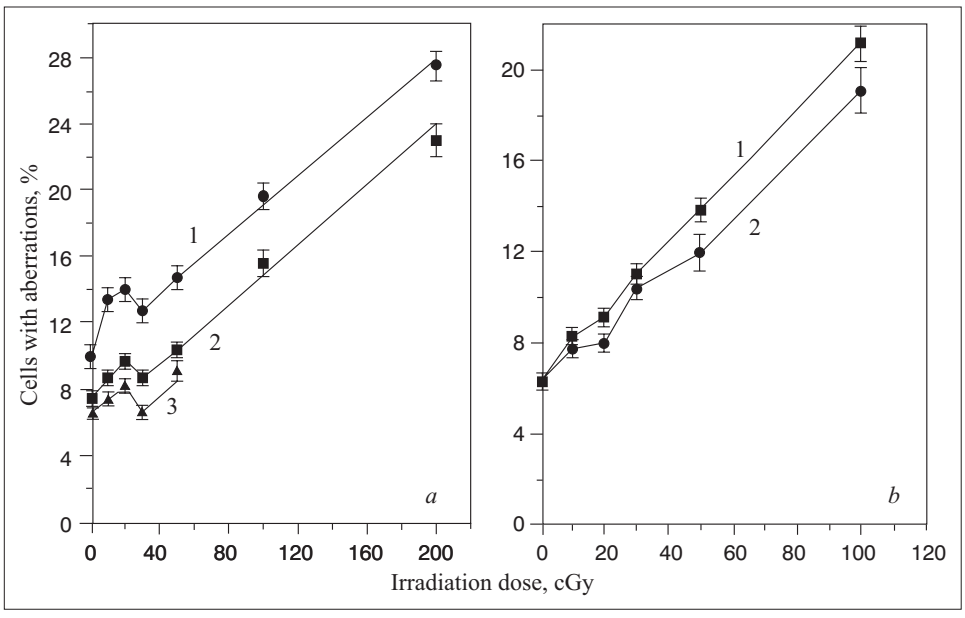
The study of stable and unstable chromosomal aberrations in human lymphocytes was continued [3]. The experiment on irradiation of human lymphocytes by the protons with the energy of 1 GeV was performed. Biotinylate- and digoxigenin-labelled total chromosomal probes were used to stain the chromosome-1 and -2 by FISH technique in spreads, fixed on microscopic slides. The stable and unstable chromosomal aberrations were analysed by FISH- and metaphase methods. The obtained data have shown that the efficiency of the protons with the energy of 1 GeV is similar to the influence of γ rays.

The study of genomic instability of HPRT-mutant clones in Chinese hamster cells (line V-79) was continued. The cells were irradiated by the protons with the energy of 1 GeV. The mutant cells were revealed and the HPRT-mutant subclones were obtained. The analysis of genomic and chromosomal instability of these mutants is being carried out. The provisional data testify the heterogeneity of mutant subclones for cytogenetical criteria. The chromosomal instability of mutant subclones is observed.

In experiments with *haploid and diploid yeast the study of induction of point mutations in eukaryotic cells* has been continued [4]. The dose-dependence of mutation induction and nature of point mutations induced by ionizing radiation was investigated. A tester system, specifically diagnosed for the six possible base-pair substitutions, was used. These strains reversed spontaneously at very low frequencies and were induced efficiently by gamma rays. The dose-response dependence features a linear-quadratic function for each base-pair substitution in diploid and haploid strains. Gamma-induced mutagenesis showed a preference for GC-AT transitions and GC-AT and AT-TA transverses in diploid strains.

The next task of this research was connected with the study of the genetic control of cell cycle arrest on mutagenesis. All living cells are exposed to a wide variety of DNA-damaging agents. When DNA is damaged, an adaptive response is triggered leading to cell cycle arrest to allow time for repair and to minimise the potentially lethal or mutagenic consequences. Cell cycle arrests are imposed by negative controls termed checkpoints that can act at various stages of cell cycle in mammalian cells as well as in yeast. Defects in checkpoint regulation can result in accumulation of mutations leading to genomic changes and neoplastic transformation. This is well examplified in the cancer-prone human disease ataxia-telangiectasia (AT). AT cells are very sensitive to gamma-rays and are also defective in post-irradiation inhibition of DNA replication and checkpoints in G1 and G2. In response to damaged DNA the tumour suppresser gene p53 activates the transcription of several genes and triggers cell cycle delay at G1 and G2 phases. The highly conserved mechanisms of DNA repair and cell cycle regulation among eukaryotes suggest the use of the yeast as a model for exploring the molecular mechanism and physiological significance in cells exposed to DNA damage. Many checkpoint genes have been identified in yeast. We identified at least three additional checkpoint genes [5,6]. Analysis of interactions between them showed that checkpoint genes don't belong to three known epistasis groups of genes of radiosensitivity. These genes are placed in two additional groups and consequently they are involved in sequential steps of different multistep biochemical pathways.

The study of spontaneous and induced deletion mutations in *bacterial cells* after irradiation was continued in



Yield dependence of Chinese hamster cells with chromosome aberrations on irradiation dose. *a* – fixing time 10 hours after irradiation (3 experiments); *b* – fixing time 3 hours after irradiation (2 experiments)

the reported period. The special test-system, used for this purpose, is based on the definition of mutations in both flanking genes: *tonB* (the stability of cells to infection by the *p80vir* phage and to the action of colicins) and *trp* (auxotroph on tryptophane). Dynamics of phenotype display of the mutations was investigated. The frequencies of occurrence of spontaneous and induced deletions (trp^--$tonB^-$) were measured. The factors affecting the SOS induction in E.coli cells such as the kind of radiation, repair genotype and cultivation conditions, were investigated. Concerning UV radiation, the molecular events leading to the SOS induction can be different at small and high doses. Particularly, the SOS-inducing lesions generated in DNA at high doses cannot be removed by constitutive repair systems as it was shown by photorectivating treatment and starvation of the irradiated suspension in buffer after exposure. It was shown that SOS induction strictly depends on the repair genotype of the cells. SOS response in the cells exposed to ionizing radiation depends on LET of the radiation. The maximum of the SOS induction corresponds to LET=20 keV/μm (Helium ions). The influence of the repair genotype on the SOS response was very similar to that observed after UV radiation.

The mathematical modelling of the SOS regulation in *Escherichia coli* cells was continued. Chromosome damage in *E.coli* bacteria or interference with DNA replication caused by ultraviolet or ionizing radiation or some chemicals results in induction of a set of physiological reactions called collectively the SOS-response. Regulation of the SOS-response induction, triggered by an inducing signal appearing after the damaging treatment, involves as its central event the interplay of the two regulator proteins, LexA (negative regulator) and RecA (positive regulator). Based on our model for SOS-response regulation, we have studied induction and turn-off of the SOS response, by simulating variations in cellular levels of the two master SOS regulators, LexA and RecA proteins. Analyses of LexA and RecA dynamics in wild-type and mutant strains, deficient in nucleotide excision repair (major cellular system for removal of ultraviolet light-induced DNA damage) help to reveal functional roles of the two regulators in the SOS-response induction. We were able to calculate dose-response curves for SOS regulatory proteins and analyse timing of the SOS regulation, which appears to be organised as a cascade of information flow through the SOS-regulatory circuit.

The study of *genetic effects of low doses of ionizing radiation* was continued in experiments with mammalian cells [7,8]. It was established that preliminary irradiation of the cells at doses of 1–20 cGy reduces the efficiency of higher consequent doses about 1.5–2 times (see the Figure). The highest values of the adaptive response were observed when the cells were irradiated by the adaptive dose in the G1 phase and by tested doses in S phase of the cell cycle.

The study of low-dose irradiation and low-dose rates of gamma radiation was also continued on yeast cells and plant cells. Earlier it had been shown that radiosensitivity of chronic irradiated cells increased when following acute irradiation and decreased at termination of the irradiation after culturing cells for 16–22 hours. We have performed investigation of the dynamics of the radiosensitivity increase. It has been shown that the cells' sensibilization does not depend on time after chronic irradiation but depends on the number of the cells' divisions occurred after the termination. The analysis of the recent investigation allows one to conclude that low-dose rate radiation does not kill cells but damages them. The damaged cells are characterized by lower speed of proliferation. The studies will be continued.

The research of gamma-ray effect at low dose rates on plant cells was aimed at the problem of linking the anomalous cell mitosis and cells' adaptive response. The result of the study shows [9] that the irradiation at low dose rates as well as at high doses leads to the increase of the amount of «rejected» seeds and causes a delay in the first mitosis. The authors observed a decrease of the chromosomal aberrations' yield and growing mitotic activity. At the same time the authors observed the response disappearance and even growth of cell radiosensitivity in the range 0÷2 cGy/h. It testifies that in the region of radiation hormesis adaptive compensation functions either disappear or are depressed. At high dose rates (about 20 cGy/h) a new adaptive cell reaction appears.

An analysis of results of epidemiological surveys of irradiated human cohorts is realised on the basis of a constructed and well-proved model of two-defence reactions. The analysis has shown [10] that the irradiation impact evaluations can differ considerably when the irradiation dose is the same, as the dose-effect dependence is determined by the radiosensitivity of an individual, or a cohort (population), by their defensive reaction reserve which in its turn depends on the medium and conditions of irradiation. A vivid example of the above-said is fully contrary to effects of Radon irradiation depending on irradiation conditions: the worst impact is for miners combining many other unfavourable factors, while the irradiation effects are favourable for house inhabitants (USA), as well as for several categories of patients who take radon baths.

The analysis of the results of the stochastic effect investigations on the cell level using the TDR model makes it possible to picture some regularities in accordance with the dose-effect dependence in the low-dose region. Growth, recession and then growth again in the aberration yield depending on the dose can be seen in the range of 10÷50 cGy, no matter what biological object it is (root meristem of barley seedlings, the HT29 cell lines of human tumour, or Chinese Hamster cells irradiated by photons). Possibly, it is the consequence of a defensive adaptive reaction, which starts at the dose of about 20 cGy.

The investigation of the application of the complex ^{211}At-Methylene Blue for *targeted radiation therapy* of pigmented melanoma was continued. This kind of therapy is founded on high affinity of MTB to melanin tumour

cells and is directed against the metastatic process, which is very characteristic of this tumour type. The degree of normal and melanoma cells damage was estimated after the application of ^{211}At in ionic form or the ^{211}At-MTB complex. The equal action efficiency of ionic ^{211}At was shown for normal Chinese Hamster cells V-79 as well as for human melanoma cells of BRO line. At the same time the efficiency of the ^{211}At-MTB action on melanoma cells is one order higher than on normal cells. This means that ^{211}At-MTB is selectively accumulated in melanin containing cells and can be used in targeted therapy of disseminated melanoma with minimal damage on normal tissues.

At the end of 1998 these investigations were separated by the project «MITRA» (within the existed scientific theme of DRRR) owing to their importance and perspective.

RADIATION PROTECTION

The radiation monitoring for occupational exposure at JINR nuclear facilities was carried out in 1998 by the automatic systems of radiation control (ASRC) and by portable instruments. The radiation field investigations in dwellings around the cyclotron U-400M were continued. The works on reconstruction of specialized ventilation of FLNR radiochemistry facilities were carried out. The modernization of the neutron measuring channels of FLNR cyclotron's complex ASRC was performed as well.

The regular environmental monitoring of soil, plants (grass), water from the river basins in Dubna vicinity, water-supply system and water effluents of enterprises allows one to assert that the environmental radiation pollution around JINR area remains constant during a long time and contains the natural radioactivity and products of global fallout only. Any contribution to radioactive pollution of the environment from the JINR nuclear facilities was not found in 1998.

In 1998, the Individual Dosimetry Service maintained dose control to 1898 persons, including 72 visitors, under individual monitoring. Their number decreased by 70 persons as compared with 1997. The yearly individual doses to the personnel did not exceed 15 mSv/yr. The highest value of the average individual dose per year among the JINR Laboratories is, as before, at FLNP and FLNR — 1.4 mSv/yr. The exceeding of the control levels of doses in Laboratories and the dose limits was not observed in 1998 as well.

EDUCATION ACTIVITY

In 1998, the process of student training at the University Center in the speciality «Radiobiology» (holder of the chair Prof. E.A.Krasavin) was successful. Three graduates and three postgraduates completed their courses at the faculty in the early 1998.

The new «Biophysics» chair was organized at Dubna International University in 1998. The chair will graduate the physical engineers in the specialty «Radiation protection of man and environment».

The work on preparation of the IAEA Regional Post-Graduated Course on Radiation Protection (the second run of which is planned to be held on the basis of JINR in autumn 1999 for states — members of the Agency from Europe and CIS) was begun.

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