

# WAYS OF PHARMACOLOGICAL PROPHYLAXIS OF STOCHASTIC AND DETERMINISTIC EFFECTS OF CHRONICAL RADIATION EXPOSURE

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## INTRODUCTION

The prophylactics of late effects of exposure is the actual medico-social problem, because now there are large groups of persons who were exposed during occupational contact and living on territories contaminated by radionuclides. Most probable consequences of external and internal chronic influence of radiation may be the increase of malignant tumour frequency, the development of secondary myelo- and immuno-depressions, the earlier forming of sclerous and destructive processes, and the acceleration of senescence. The role of damages in immune system was not yet understood in pathogenesis of the late effects of radiation, but there are evidences that the decreasing of the immunologic supervision in period of forming the consequences of radiation influence enables to realize the cancerogenic effect of radiation (1,2).

The purposes of this investigation are to decrease the frequency or to prevent the development of radiation consequences dangerous for health and life by using the method of modification of radiogenic damages in hemopoietic and immune systems by applying the pharmacological preparations with immunomodulating effects. The investigation tasks include: the study of modifying influence of pharmacological substances with different mechanisms of effect: myelopid (immunomodulating, and regulatory),  $\beta$ -carotin, *Calendula officinalis* (immunomodulating, and antioxidant), lipamid (detoxicating); the separate or complex applications of these substances; and the development of the optimum medico-prophylactic schemes. The advantages of these indicated preparations in comparison with the known (T-activin, thymogen, cytokines, etc.) are the absence of contraindications and the possibility to use *per os*.

## MATERIALS AND METHODS

The work was conducted on 2 species of laboratory animals (*Wistar* rats, and *CBA* mice) under three models of chronic radiation damages, following the incorporation of plutonium-239 (polymer nitrate or citrate, single injection by amount of 92.5 kBq/kg), and of tritium oxide (HTO, daily drinking water intake, total dose of 9 Gy for 6 or 3 months, dose rates of 4.5 and 9.2 cGy/day), or the long-time fractionational external  $\gamma$ -exposure to cesium-137 (dose of 6 Gy for 6 weeks, or for 3 weeks with dose rate 20 cGy per day for 3 hours, the exposure during 5 day per week with interval of 3 or 10 days).

The medico-prophylactic courses were begun in 0.7, 2, or 5 months after beginning of external exposure; in 1 or 6 months after HTO intake; and in 0.2, 2, or 6 months after plutonium-239 intake. Myelopid (MP), produced at the Immunology Institute, Moscow, was injected hypodermicly one-time per week or per month giving 0.6 mg/kg or 2.0 mg/kg, respectively, and making 3-14 injections per 1 or 2 courses.  $\beta$ -carotin (produced by "Vitamins" SPI, Moscow) was received by animals together with foods (curds, olive oil) in amount of 7 mg/kg during 4 months. The *Calendula officinalis* was received with drinking water by mice in amount of 12 ml/kg, and by rats in amount of 5.6 ml/kg. The tablets of lipamid were taken with the crude for mice in amount of 15

mg/kg per day, and for rats in amount of 7.2 mg/kg per day. The complex of myelopid, lypamid, and *Calendula* was received by animals in the same amount, as separately.

The evaluation of modifying effects of medicinal preparations was conducted after exposure and 1 or 2 courses of immuno-therapy for the following criteria: the number of stem cells (SFU<sub>s-8</sub>, SFU<sub>s-12</sub>); of karyocytes in bone marrow and in immunity organs; of T- and B-lymphocytes, plaque-forming units in spleen (PFU - integral index of humoral immunity); of peritoneal macrophages, by taking the functional activity of lymphocytes, macrophages, natural killers, RBTL, the content of leukocytes in blood as well as by results of autopsy study after animal death.

The processing of data was conducted by general statistical methods with estimate of statistical reliability of differences equal to  $p \leq 0.05$ , as threshold of unerring prognoses.

## RESULTS AND DISCUSSION

Chronic radiation damage under indicated models of influence may be characterized as having the phases. The traits of damages in hemopoietic and immune systems depended from kinds of ionizing radiation or from plutonium compositions, dose rate, and the total dose of exposure, the duration of influence, evenness of exposure. The development of myelodepression, hypoplasia of lymphoid organs, and immuno-deficiency state were being observed under impact of HTO or plutonium-239 polymer nitrate. It was found out the deep suppression of humoral immunity (decrease of PFU up to 10% of intact control), the decreasing of activity of cellular immunity effectors by 10-30%. The damages of immune processes were less expressed, and recovered to normal values in 3-6 months of observing in case of external exposure or of plutonium citrate injection. For all kinds of ionizing radiation, the most deep and stable changes (up to 10% of norm and below) were indicated in the stem cell compartment under considering all studied models of radiation damage, and full recovery of these cells' number was not registered for period of observation.

Leukopenia was not long after all kinds of radiation influence, the lymphopenia and hypoplasia of lymphoid tissue depended from the decreasing of population of both T- and B-lymphocytes. The value of proliferative ability damage increased with increasing dose of even exposure.

The application of pharmacological preparation under long-term influence of radiation allows to decrease the depth of immuno-deficiency and myelodepression, and all the tested medicinal preparations have immunomodulating effect: the increase of stem cell content at 1.5-2.5 times; the increase of the antibody-producers at 1.5-4 times; the decrease of hypoplasia of lymphoid organs at 1.5-2.5 times; the increase of functional activity of cellular immunity effectors by 10-50% in comparison with exposed animals that were not treated). The stimulating effect of immunomodulators was more expressed under significant damage of radiosensitive organs and tissues, but the same effect was indicated in case of using substances when there was full recovery of immune reactions. It was found out that the indicated modulating effect of preparations was pronounced mainly in 2-3 months after medico-prophylactic course, and more constant influence of medicinal substances on recovery processes was registered in the stem cell compartment. The regulatory effect of myelopid was being observed during the recovery of immunity indexes, and it was higher than for the intact control. The most expressed effect was determined in case of complex application of preparations (myelopid, *Calendula officinalis*, and lypamid; or myelopid and  $\beta$ -caratin) for both external and internal exposures. Chronic effect of incorporated tritium or plutonium polymer nitrate caused the decrease of the average lifetime (ALT) by 10% and the increase of malignant tumour frequency at 2 times due to mainly the increasing

of outcomes of myeloleukemia, lung cancer (HTO), liver tumour, and ostersarcoma (plutonium-239).

The medico-prophylactic course of myelopid provided the decrease of common number of malignant tumours at 1.5 times ( $p < 0.05$ ), including the frequency of lung cancer that decreased at 1.7 times up to spontaneous level; the myeloleukemia decreasing at 3.6 times; and tumours of liver and ostersarcomas decreasing up to the spontaneous level. The receiving of  $\beta$ -carotin enabled to decrease at 1.5 times (lower than spontaneous level) the frequency of lung cancer, and at 3 times the myeloleukosis induced by tritium. In case of fractionational  $\gamma$ -exposure (dose of 3 Gy), the decrease of ALT was not find out, however, the malignant tumour frequency increased at 6 times due to the increase of leukemia and liver cancer. Myelopid applications, separately or in complex with  $\beta$ -carotin, led to the decrease of leukemia frequency up to spontaneous level, and of liver cancer at 2.5 times.

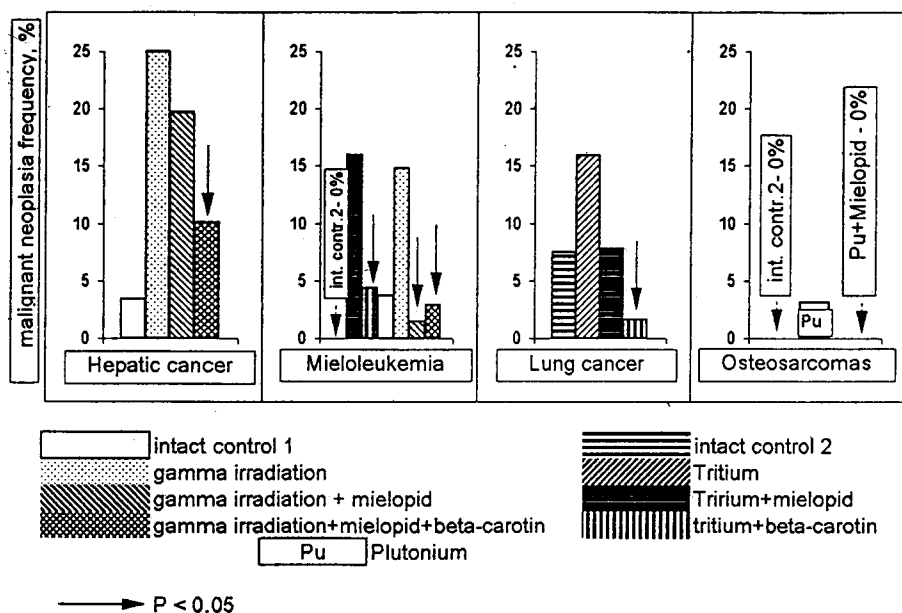


Figure 1  
Pharmacological prophylaxis of malignant neoplasia after internal (Pu and Tritium) and external (Cs-137) irradiation in mice

Thus, pharmacological preparations with immunomodulating effect may decrease the level of damages of immunity organs, promote the more full recovery of hemopoietic and immune systems, and these functions, increasing the immune control that allows to decrease the malignant tumoural growth or to prevent the developing of the radiogenic malignant neoplasms.

## REFERENCE

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2. Kirillova E.N., Revina V.S., Sokolova S.N. *Radiobiology* 31, 357-360 (1991).