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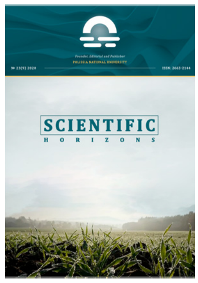

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Influence of Ionizing Radiation on the Allergic Reactivity of Tuberculosis-Infected Laboratory Animals

Volodymyr Kassich[1*], Oksana Kasianenko[1], Volodymyr Zazharskyi[2], Ivan Yatsenko[3], Zhanna Klishchova[4]

[1]Sumy National Agrarian University
40000, 160 H. Kondratiev Str., Sumy, Ukraine

[2]Dnipro State Agrarian and Economic University
49000, 25 Serhiy Yefremov Str., Dnipro, Ukraine

[3]Kharkiv State Veterinary Academy
62341, 1 Akademichna Str., v. Mala Danylivka, Ukraine

[4]Medical Institute of Sumy State University
40000, 31 Sanatorna Str., Sumy, Ukraine

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Abstract. Allergic examination using PPD-tuberculins is the main method of life-time tuberculosis diagnostics in farm animals and poultry. However, it is known about a decrease in the diagnostic value of allergic reactions after irradiation of animals, the occurrence of non-specific, pseudo-allergic reactions. One of the reasons for the manifestation of non-specific reactions may be autosensitisation (autoallergisation) of the body by the breakdown products of personal tissues, which is especially pronounced with radiation damage. Ionizing radiation affects the manifestation of tuberculin sensitivity, the course of tuberculosis and autoimmune processes in the body. Differential diagnostics of non-specific tuberculin reactions remains not yet a fully solved problem, although there are many tests for its implementation. After the accident at the Chernobyl nuclear power plant, a considerable number of animals remained in the adjacent territories contaminated with radioactive substances, including those infected with the causative agent of tuberculosis and atypical mycobacteria. It is known that irradiation leads to autosensitisation of the body by the breakdown products of its own tissues and the development of non-specific pseudoallergic reactions to heterologous allergens. Therefore, work was carried out to study the allergic reactivity of tuberculosis patients and laboratory animals sensitised with atypical mycobacteria irradiated with gamma radiation (200 guinea pigs). It was established that 14-60 days after infection with tuberculosis pathogens, 90-100% of cavies developed allergic reactions to PPD-tuberculin for mammals and poultry, mainly to a homologous allergen. Allergic reactivity persisted until 90 days of the study. After exposure to sublethal (non-lethal) doses of gamma rays, infected and intact cavies developed non-specific reactions to tuberculin and heterologous allergens: mallein and brucellin. In cavies uninfected with the causative agent of tuberculosis, 7 days after gamma radiation exposure, non-specific reactions to mycobacterial allergens were observed at a dose load of 200 R in 16.6%; 150 R – 5.3% in the group, and after 27 days in irradiated doses of 50 R and 100 R in 25% and 33% of the studied animals, respectively. Isolated reactions to brucellin and mallein occurred in animals infected with the causative agent of tuberculosis and intact animals 60 days after irradiation with doses of 50 R, 100 R and 150 R. The manifestation of non-specific allergies in irradiated animals depended on the radiation dose rate and radiosensitivity of the animals

Keywords: tuberculin, heterologous allergens, gamma radiation, mycobacteria, allergic studies

Corresponding author

INTRODUCTION

Tuberculosis has a special place among infectious diseases of farm animals since this disease not only causes considerable economic losses to animal husbandry but also poses a constant danger to human health. According to WHO, tuberculosis is currently the most common infection in the world [1-4]. Human and animal tuberculosis is widespread and is registered in many countries. Among domestic animals, tuberculosis most often occurs in cattle. The main method of intravital diagnostics of tuberculosis is an allergic study using PPD-tuberculins for mammals and poultry. Therewith, literature sources provide information indicating a decrease in the diagnostic value of allergic reactions after irradiation of animals [5; 6]. One of the reasons for the development of a non-specific allergy to tuberculin can be not only sensitisation by microorganisms of the genus *Mycobacterium* but also autoallergisation (autosensitisation) of the body by the breakdown products of its own tissues. Several researchers state that this is the reason for the simultaneous existence of specific and non-specific reactions in tuberculosis [7]. Tissue breakdown processes are observed when exposed to ionizing radiation, an indicator of which is an increase in urinary excretion of deoxycytidine [8-14]. The mechanism of changing the allergic reactivity of an irradiated organism is still poorly understood. It was proved that it is based on a violation of the general immunological state of the body, in particular, an increase in the appearance of autoantibodies [15; 16]. Non-specific reactions to tuberculin in animals sensitised by atypical mycobacteria are usually called paraallergic (paraspecific), and reactions caused by other factors (including unknown ones) are called pseudoallergic [17]. Differential diagnosis of non-specific tuberculin reactions remains not yet a completely solved problem, although there are several tests for its implementation (simultaneous allergic test, CSC, etc.). An important reason for the manifestation of non-specific reactions can be autoallergisation of the body by decay products of its own tissues, which is especially pronounced in radiation damage [18-21]. Ionizing radiation affects the manifestation of tuberculin sensitivity, the course of tuberculosis, and autoimmune processes in the body [22-26]. The widespread use of nuclear energy in the national economy is of great importance for the development of the domestic economy. However, radiation pollution of the biosphere as a result of the Chernobyl accident causes increasing exposure of populations of living organisms. Long-term contacts of humans, farm animals and other biological objects with sources of ionizing radiation of various nature have become a reality.

As a result of the Chernobyl accident, more than 144 thousand hectares of agricultural land were withdrawn from crop rotation. In total, about 10 million hectares are contaminated with radionuclides, of which more than 3 million are farm land [1]. In Ukraine, the territory of 17 regions is contaminated with radionuclides. The contaminated areas contain a considerable number of farm animals, including those with tuberculosis or sensitised by atypical mycobacteria. Ionizing radiation can affect both the causative agent of an infectious disease and the susceptible organism. The degree of such exposure depends on the character of the radiation, the dose, its power, and many other factors. Therefore, the situation that arose after the Chernobyl accident required a deep study since the effect of radiation on the links of the epizootic process could lead to unforeseen changes in the epizootic and epidemic situation. In this regard, the determination of the epizootic value of mycobacteria (pathogens of tuberculosis of animals, poultry, humans and atypicals) under the influence of ionizing radiation, the study of the features of the biological effect of ionizing radiation of different intensities on the animal body, the introduction of optimal measures and means for the diagnostics and control of tuberculosis in radioactively contaminated territories have gained particular importance. Information on changes in allergic reactivity and features of clinical and immunological manifestations of animal tuberculosis against the background of ionizing radiation exposure is limited and is usually obtained in experiments on experimental models of laboratory animals. Until recently, the epizootic situation of animal tuberculosis in radioactively contaminated regions of Ukraine was not monitored. Methods for diagnosing tuberculosis in livestock kept in radioactively contaminated regions of the country have not been optimised.

Nowadays, when man-made disasters are a reality, the study of allergic diagnostics of animal tuberculosis is relevant, especially for Ukraine, on the modern territory of which the Chernobyl nuclear power plant is located with the adjacent exclusion territory and radionuclide-contaminated regions where productive animals are kept and used.

The purpose of the paper is to study the effect of irradiation on the allergic reactivity of laboratory animals.

MATERIALS AND METHODS

To study the effect of ionizing radiation on the specificity of allergic reactions, an experiment was conducted on 200 cavies weighing 300-350 g, selected according to the analogue method. The animals were divided into 5 groups of 40 heads each. To exclude natural tuberculosis of all animals, an allergic sample with mammalian PPD-tuberculin and an allergen from atypical mycobacteria was previously studied (30 days before irradiation) [27]. At the same time, brucellin (produced by Kherson biological factory) and mallein (produced by Kursk biological factory) were administered at a dose of 0.1 cm^3 intradermally. The purpose of introducing allergens that are not specific to tuberculosis and animal species (cavies), whose body cannot be sensitised to brucellosis and equinia pathogens by natural or experimental infection, was to study the possibility of developing non-specific pseudoallergic reactions in irradiated animals against the background of autosensitisation of their body by decay products of their own tissues due to radiation damage. In addition, the purpose was to establish whether irradiation and the resulting immunodeficiency state will contribute to the occurrence and development of characteristic pathoanatomical changes in cavies infected with poultry tuberculosis pathogen (*M. avium*). *M. avium,* according to the Ranion classification (1959), is classified as atypical mycobacteria of the third group: non-photochromogenic mycobacteria (achromous or have a yellow tint regardless of lighting). *M. avium* is pathogenic for poultry, rabbits and pigs, not pathogenic for cavies, cattle, but when administered to immune animals causes an immunobiological restructuring of the body, sensitisation and the occurrence of paraallergic reactions to mycobacterial allergens (PPD-tuberculin for mammals, PPD-tuberculin for poultry, and an allergen from atypical mycobacteria (AAM), differentiation of which is carried out using a simultaneous allergic test [27].

To solve the objectives set in the work, four groups of animals were separately irradiated with total gamma radiation in doses of 0.0129 C/kg (50 R); 0.0258 C/kg (100 R); 0.0387 C/kg (150 R), and 0.0516 C/kg (200 R) with a dose rate of 2.85 R/sec on the IGUR gamma emitter (radiation source ^{137}Cz). Irradiated and intact (unirradiated) cavies were divided into two equal groups of 100 animals each. Animals of the first group were examined one day after radiation treatment by a simultaneous allergic sample with mammalian PPD-tuberculin and an allergen from atypical mycobacteria [27]. 7 days after irradiation, animals of this group (5-6 irradiated doses of 0.0129 C/kg (50 R); 0.0258 C/kg (100 R); 0.0387 C/kg (150 R), and 0.0516 C/kg (200 R) and intact) were infected with mycobacterium cultures. Cultures of bovine (*M. bovis No. 8),* human (*M. tuberculosis,* strain *M*), and bird (*M. avium 780*) species of mycobacteria from the Museum of the tuberculosis laboratory of the VIEV were used. Infectious material was administered subcutaneously to each laboratory animal (cavies) in the groin area according to the generally accepted method of 1 mg of raw bacterial mass suspended in 1 ml of sterile isotonic solution of *NaCl*. Infected animals and cavies of the other group (not infected, irradiated and intact) were examined with a simultaneous allergic test 7 days after exposure to ionizing radiation. 14 days after irradiation, uninfected animals (5 cavies from each group exposed to the specified doses and intact) were inoculated with the same cultures of tuberculosis pathogens (*M. bovis, M. tuberculosis* and *M. avium)* in the same doses.

That is, after total gamma radiation exposure in doses of 0.0129 C/ kg (50 R), 0.0258 C/kg (100 R), 0.0387 C/kg (150 R), and 0.0516 C/kg (200 R), experimental animals were infected with cultures in two stages: 7 and 14 days after radiation exposure (75 animals each) were infected with *M. bovis, M. tuberculosis* and *M. avium*. 50 cavies (10 irradiated with doses of 50 R (0.0129 C/kg); 100 R (0.0258 C/kg); 150 R (0.0387 C/kg), and 200 R (0.0516 C/kg) and intact) were not infected with mycobacteria and were used as a control group. Before the infection (1 and 7 days after irradiation), experimental animals were examined by a simultaneous allergic test with PPD-mammalian tuberculin and an allergen from atypical mycobacteria.

14, 45 and 90 days after infection, experimental animals were examined with simultaneous allergic testing, as well as brucellin and mallein (to study the possibility of non-specific pseudoallergic reactions against the background of autosensitisation of the body of irradiated laboratory animals with decay products of their own tissues during radiation damage), which were administered intradermally in a dose of 0.1 ml using separate labeled syringes in the centres of depilated (hairless) skin areas on the sides of cavies. The results of allergic tests were considered 24 and 72 hours after drug administration, entered in the table and analysed using statistical methods.

The work was carried out based on VIEV (Moscow) and the All-Russian Research Institute of Farming Radiology and Agroecology (Obninsk). The results are submitted for printing for the first time. All the experiments described in the paper were conducted in accordance with the current legislation of Ukraine and general international ethical rules and requirements for the use of vertebrates in medical experiments – conclusion of the SNAU Bioethics Commission, Protocol No. 5 dated May 17, 2021 [28-30].

RESULTS AND DISCUSSION

During allergic studies with a simultaneous allergic test 7 days after exposure to ionizing radiation, 2 out of 19 uninfected animals irradiated with doses of 150 R (0.0387 C/kg) and 3 out of 18 irradiated with a dose of 200 R (0.0516 C/kg) showed reactions at the site of administration of mycobacterial allergens. Therewith, reactions to tuberculin were: in the group irradiated with a dose of 150 R (0.0387 C/kg) – in one animal (5.3% of the studied); 200 R (0.0516 C/kg) – 1 (5.5%). The reaction to an allergen from atypical mycobacteria was noted: in the group irradiated with a dose of 150 R (0.0387 C/kg) – 1 animal (5.3% of the studied), 200 R (0.0516 C/kg) – 2 animals (11.5%).

Notably, 72 hours after the administration of allergens in two cavies with an irradiated dose of 200 R (0.0516 C/kg) at the site of administration of an allergen from atypical mycobacteria, cold, painless swellings of dense consistency in the form of peas with a diameter of 9x9 and 5x5 mm were observed, respectively, which indicates the possibility of developing non-specific reactions to mycobacterial allergens in irradiated animals at a later time compared to specific tuberculin ones.

14 days after infection (20 days after irradiation), an allergic study of cavies infected 7 days after general gamma radiation was conducted. Therewith, it was established that among cavies irradiated with a dose of

0.0129 C/kg (50 R), infected with *M. bovis* and *M. tuberculosis*, isolated reactions to mammalian PPD-tuberculin were reported after 24 and 48 hours (16.7 and 33% ±0.2 mm responded, respectively). The diameter of the papule at the injection site in cavies infected with *M. bovis* was 9.0±33.0 mm, in infected with *M. tuberculosis* – 9.9±2.5 mm. For those infected with *M. avium*, no allergic reactions to allergens were observed in infected and uninfected animals exposed to a dose of 0.0129 C/kg (50 R).

Among cavies irradiated with a dose of 0.0258 C/kg (100 R) and infected with *M. bovis*, no allergic reactions to tuberculin were recorded. In single animals (20% of the studied) infected with *M. tuberculosis* and *M. avium*, reactions to tuberculin with a papule diameter of 7.1-9.2 mm were observed after 24 hours. There were no allergic reactions in uninfected animals exposed to this dose.

In the groups irradiated with doses of 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg), mass death of animals was noted (from 66.7 to 100%). At the autopsy, hemorrhagic diathesis was noted in the form of extensive hemorrhages of various forms in the mucous and serous membranes of the thoracic and abdominal cavities and parenchymal organs, as well as the serous-hemorrhagic exudate in the cavities. No allergic reactions to the administration of allergens were observed in animals.

Isolated allergic reactions were observed among unirradiated infected animals:

- in 10% of cavies infected with *M. bovis* – on PPD-tuberculin for mammals (papule diameter from 15 to 29 mm);
- in 50% of those infected with *M. tuberculosis* (papule diameter 17±1.25 mm);
- in 30% of infected with *M. avium* (papule diameter 8.0±2.0 mm).

No reactions to the allergen were observed in uninfected animals. That is, 14 days after infection, animals infected with tuberculosis pathogens 7 days after irradiation in doses of 0.0129 C/kg (50 R) and 0.0258 C/kg (100 R) and not irradiated developed isolated reactions to mycobacterial allergens. Infected animals exposed to doses of 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg), as well as uninfected, both irradiated and intact, did not respond to the administration of allergens.

The results of accounting for a simultaneous allergic test of infected cavies 14 days after irradiation are shown in Table 1.

***Table 1**. Results of an allergic study of cavies 14 days after infection and 28 days after irradiation*

Radiation dose (R/C/kg)	Type of pathogen	Number of animals with allergic reactions	Reaction intensity (mm) to: PPD-tuberculin for mammals	Reaction intensity (mm) to: KAM
1	2	3	4	5
50/0.0129	*M. bovis*	5	10.0±0.5	
		3		6.3±2.5
50/0.0129	*M. tuberculosis*	3	10.0±0.5	
		2		6.3±2.5
50/0.0129	*M. avium*	2	8.0±1.2	
		3		8.8±1.1
50/0.0129	Not infected	1	9×9	
		–		
100/0.0258	*M. bovis*	4	10.1±0.5	
		2		6.1±1.6
100/0.0258	*M. tuberculosis*	3	9.0±1.5	
		2		6.4±2.2
100/0.0258	*M. avium*	2	8.0±1.1	
		3		8.8±1.2
100/0.0258	Not infected	1	8×6	
		–		
150/0.0387	*M. bovis*	1	10×10	
		–		
150/0.0387	*M. tuberculosis*	2	8.2±1.7	
		1		6×6
150/0.0387	*M. avium*	–		
		–		
150/0.0387	Not infected	–		
		–		

Table 1, Continued

Radiation dose (R/C/kg)	Type of pathogen	Number of animals with allergic reactions	Reaction intensity (mm) to: PPD-tuberculin for mammals	Reaction intensity (mm) to: KAM
200/0.0516	*M bovis*	1	5×5	
		–		
200/0.0516	*M. tuberculosis*	–		
		–		
200/0.0516	*M. avium*	–		
		–		
200/0.0516	Not infected	–		
		–		
Not irradiated	*M. bovis*	4	7.7±1.3	
		1		7×7
	M. tuberculosis	2	6.8±1.2	
		–		
	M. avium	–		
		–		
	Not infected	–		
		–		

The study was conducted 14 days after infection (28 days after irradiation of animals). From the table materials, it can be seen that cavies irradiated with doses of 50 R (0.0129 C/kg) and 100 R (0.0258 C/kg) and infected with *M. bovis* and *M. tuberculosis,* had intense reactions to the introduced allergens in the form of hyperemia and extensive infiltrates. Animals mainly reacted to mammalian tuberculin (75-100%), while reactions to an allergen from atypical mycobacteria were observed in 50-66% of cases or were absent. In terms of the intensity of manifestation, reactions to tuberculin were larger (papule diameter 10.0±0.5 mm) than to an allergen from atypical mycobacteria (6.3±025 mm).

In the groups of uninfected animals exposed to total gamma radiation at doses of 50 R (0.0129 C/kg) and 100 R (0.0258 C/kg), two cavies (one in each group) responded to tuberculin after 48 hours. Reactions were dense consistency, painless infiltrates at the injection site (papule diameter 9x9 and 8x8 mm, respectively), skin hyperemia was not noted. In cavies irradiated at doses of 50 R (0.0129 C/kg) and 100 R (0.0258 C/kg) and infected *M. avium,* positive reactions were observed mainly on KAM. Reactions were observed in 66.7-80% of the experimental animals, with a papule diameter of 8.8±1.1 mm. Positive reactions to mammalian tuberculin were observed in 33.3-40% of the studied animals, the infiltrate diameter was 8.0±1.2 mm.

Among animals irradiated with doses of 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg), deaths were recorded (from 33.3 to 100% in the group). At the autopsy, the hemorrhagic syndrome was observed with the serous effusion in the body cavities. In groups of animals irradiated with doses of 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg), infected with *M. bovis,* positive reactions to mammalian PPD-tuberculin were noted. Therewith, in the group irradiated with a dose of 150 R (0.0387 C/kg), one cavy remained and reacted during the study (papule diameter – 10.0 mm). In the group irradiated with a dose of 200 R (0.0516 C/kg), the reaction was observed in one of the three studied animals (papule diameter – 5.0 mm).

In the group of irradiated cavies with a dose of 150 R (0.0387 C/kg) and infected with *M. tuberculosis* at the time of the study, two animals remained alive. Both responded positively to mammalian administration of PPD-tuberculin (papule diameter – 8.2±1.2 mm). One cavy reacted to KAM (papule diameter – 6.0 mm). In the group of irradiated with a dose of 150 R (0.0387 C/kg) and infected with *M. avium*, one of the two animals left alive on the day of the study responded to KAM with a papule diameter of 5.0 mm.

Among the unirradiated cavies infected with *M. bovis* and *M. tuberculosis,* positive reactions to tuberculin were observed. In animals infected with *M. avium*, no allergic reactions were observed. Thus, from 50 to 100% of infected animals reacted to specific allergens 14 days after exposure to various doses of gamma radiation (with the exception of those infected with *M. avium*). At the same time, uninfected cavies irradiated with doses of 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg) had single 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg), non-specific reactions to tuberculin.

Based on a comparison of the results of an allergic study of experimental animals infected at intervals of 7 and 14 days after exposure to ionizing radiation, it can be argued that 2 weeks after the administration of infectious material, contaminated animals, both irradiated and intact, showed an infectious allergy to specific allergens. Therewith, in groups of animals infected with mycobacteria 7 days after irradiation, 16.7-50% reacted positively, while among animals infected 14 days after irradiation – 50-100%, which indicates a faster development of the infectious process in animals infected 2 weeks after irradiation, when the symptom complex of pronounced clinical signs of radiation sickness manifests itself more intensively, as evidenced by the mass death of cavies (up to 100% in groups irradiated 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg)) with a picture of hemorrhagic syndrome and progressive changes in the hematopoietic organs.

That is, 14-21 days after irradiation among cavies irradiated with doses of 150 R (0.0387 C/kg) and 200 R (0.0516 C/kg), mass death of animals was noted (from 66.7 to 100% in the group). At the autopsy, pathoanatomical changes characteristic of radiation damage were noted: hemorrhagic diathesis in the form of extensive hemorrhages on the mucous membranes and in the serous membranes of the thoracic and abdominal cavities, as well as the presence of serous-hemorrhagic exudate in the cavities.

Starting from 21 days after infection in dead irradiated and unirradiated cavies infected with *M. bovis* and *M. tuberculosis*, tuberculosis-specific lesions of varying intensity were noted: exhaustion, ulcers at the culture injection site, and at autopsy, a considerable increase in the liver and spleen was observed with the presence of foci of caseous necrosis in them (Fig. 1-4). Among the cavies infected with *M. avium*, no such lesions were observed.

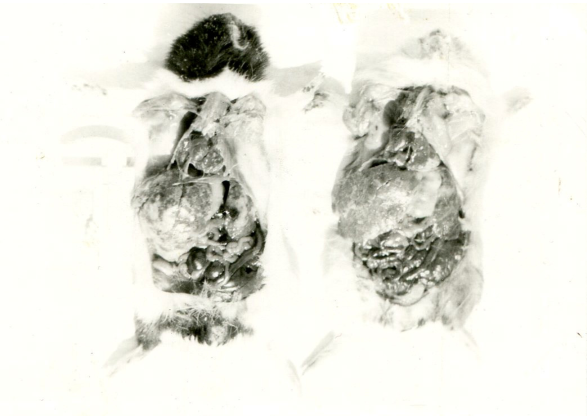

***Figure 1**. Generalised tuberculosis of cavies that died 25 days after infection with M. bovis, irradiated with gamma radiation at a dose of 150 R (0.0387 C/kg). Considerable enlargement of the liver, spleen, foci of caseous necrosis*

***Figure 2**. Considerable enlargement of the spleen, miliary tuberculosis in cavy exposed to a dose of 200 R (0.0516 C/kg), which died 25 days after an infection with M. tuberculosis*

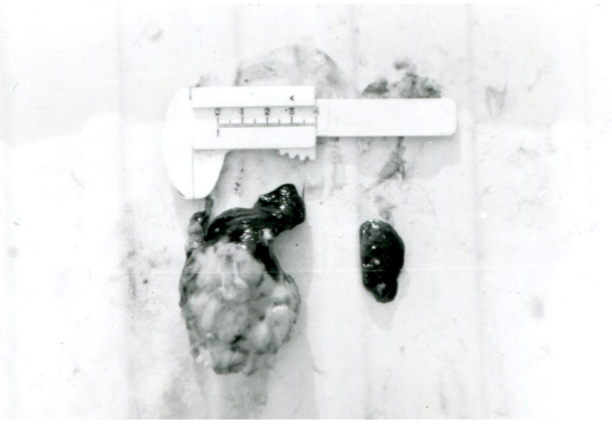

***Figure 3**. The spleen of the cavy deceased 31 days after an infection with M. bovis (left). On the right is the spleen of a cavy infected with M. avium at the same time. Irradiation with a dose of 150 R (0.0387 C/kg)*

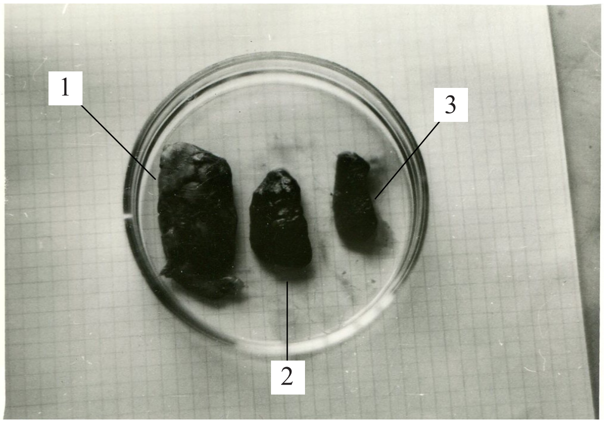

***Figure 4**. Spleens of cavies irradiated with a dose of 50 R (0.0129 C/Kg), who died after the twentieth day after infection: 1 – M. bovis; 2 – M. tuberculosis; 3 – M. avium*

Figure 4 shows that the seals, the appearance of tubercles and necrotic foci with caseous contents are noticeable in the first two cases. In the third case, there are no tuberculosis lesions.

Notably, 25-33.3% of uninfected animals exposed to doses of 50 R (0.0129 C/kg) and 100 R (0.0258 C/kg) had pseudoallergic reactions to tuberculin (non-specific allergy) 27 days after irradiation.

60 days after the beginning of an experiment allergic reactions to mammalian PPD-tuberculin were observed among animals irradiated with a dose of 50 R (0.0129 C/kg) in groups infected with *M. bovis* and *M. tuberculosis*. Out of the nine cavies infected with *M. bovis,* reactions were observed in six (66.7%), the papule diameter was 11.8±1.1 mm. Out of eight animals infected with *M. tuberculosis*, 7 reacted positively to tuberculin, the papule diameter was 21.3±1.6 mm. In the group contaminated with *M. avium*, seven of the eight cavies that remained alive at the time of the study showed reactions to PPD-tuberculin for poultry, the papule diameter was 13.6±1.2 mm. Therewith, isolated pseudoallergic reactions to brucellin and mallein (non-specific allergy) were noted in the studied animals. Therewith, in the group of animals infected with *M. tuberculosis*, three cavies with a papule diameter of 9.7±0.2 mm reacted to brucellin. In the group infected with *M. avium,* two cavies reacted to brucellin, the papule diameter was 8x8 mm, and three reacted to mallein (diameter 7.0±0.7 mm). In the group of uninfected animals irradiated with a dose of 50 R (0.0129 C/kg), one of the ten cavies had a reaction to brucellin (diameter 10 mm).

In the group of cavies exposed to radiation at a dose of 100 R (0.0258 C/kg) and infected with *M. bovis,* two out of five animals responded positively to mammalian tuberculin (papule diameter 13.0±0.2 mm). In the group infected with *M. tuberculosis,* all animals responded to drug administration (papule diameter 17.5±0.7 mm). Among those infected with the poultry tuberculosis pathogen, all animals responded to PPD-tuberculin for poultry. One cavy had a reaction in the form of an infiltrate with skin redness with a diameter of 10 mm at the brucellin injection site. No allergic reactions were observed in control (uninfected) animals exposed to a dose of 100 R (0.0258 C/kg).

Among those irradiated with a dose of 150 R (0.0387 C/kg) from the group of animals infected with *M. bovis* on the day of the study, one guinea pig remained alive, which developed an allergic reaction in the form of an infiltrate with erythema of the skin with a diameter of 5 mm 48 hours after the administration of PPD-tuberculin for mammals. Out of those infected with *M. tuberculosis,* two cavies that reacted to mammalian tuberculin (papule diameter 20.0±1.6 mm) remained alive. One of these animals had a skin allergic reaction to brucellin in the form of an infiltrate with skin redness of size 8×6 mm.

All studied cavies infected with *M. avium* reacted to PPD-tuberculin for poultry (papule diameter 17.1±0.8 mm). One animal showed a reaction to brucellin (infiltrate with a diameter of 5 mm). All control (uninfected) animals exposed to a dose of 150 R (0.0387 C/kg) died during the study. In the group irradiated with a dose of 200 R (0.0516 C/kg) and infected with *M. bovis* on the day of the study, no cavies remained alive. In the group of cavies infected with *M. tuberculosis,* only one remained alive. The animal was exhausted, an open abscess was observed at the site of infection. The animal did not respond to the administration of allergens (a state of anergy).

In the group of cavies irradiated with a dose of 200 R (0.0516 C/kg) and infected with *M. avium,* two animals remained alive. One of them showed a reaction to PPD-tuberculin for poultry, the papule diameter is 20 mm. All uninfected animals from the group exposed to a dose of 200 R (0.0516 C/kg) on the day of the study died.

In the group of unirradiated, infected with *M. bovis* at the time of the allergic study, only one cavy remained alive, which responded to the administration of PPD-tuberculin for mammals, with a papule diameter of 16 mm.

Out of nine animals infected with *M. tuberculosis,* skin allergic reactions in the form of large infiltrates with a diameter of 22.0±2.2 mm with areas of ischemia and necrosis in the centre were observed in eight unirradiated animals at the site of tuberculin administration. In 40% of the studied animals, skin lesions were observed in the form of abscesses and ulcers at the site of administration of infectious material.

In the group of unirradiated animals, contaminated with *avium,* allergic skin reactions with a diameter of 13.0 ± 2.1 mm were observed in 6 out of 7 studies at the injection site of PPD-tuberculin for poultry. All the cavies were well-fed and active. No allergic reactions were recorded in the group of unirradiated and uninfected animals.

Thus, reactions to homologous allergens were observed 60 days after exposure (48-53 days after infection) and most (50-100%) infected irradiated and intact animals. Reactions were intense in the form of hyperemia and extensive infiltrates, often with areas of ischemia and necrosis. Exhausted animals with noticeable skin lesions in the form of ulcers or abscesses did not respond to allergens (a state of anergy).

In infected and intact animals exposed to doses of 50 R (0.0129 C/kg), 100 R (0.0258 C/kg) and 150 R (0.0387 C/kg), isolated reactions to the administration of heterologous bacterial allergens (brucellin and mallein) were observed. Therewith, 12.5% of the total number of animals exposed to brucellin reacted, including 20% of those exposed to a dose of 50 R (0.0129 C/kg), 3.5% of those infected with a dose of 100 R (0.0258 C/kg), and 30% of those exposed to a dose of 150 R (0.0387 C/kg) in groups infected with *M. tuberculosis* and *M. avium*. 8.3% of irradiated animals reacted to mallein, while reactions were observed only in the group of cavies exposed to a dose of 50 R (0.0129 C/kg).

Thus, after the infection with tuberculosis pathogens, laboratory animals developed allergic reactions to homologous allergens (PPD tuberculin and an allergen from atypical mycobacteria). Non-specific reactions to mycobacterial allergens were observed in 5.6-33% of animals not infected with the causative agent of tuberculosis after irradiation. Cavies infected with the causative agent of tuberculosis experienced isolated reactions to heterologous allergens: brucellin and mallein 60 days after irradiation. The manifestation of non-specific allergies in irradiated laboratory animals depended on the radiation dose. After infection of cavies irradiated with various doses of radiation and not irradiated with the causative agent of poultry tuberculosis, starting from 14 days after the administration of infectious material, the animals developed delayed-type hypersensitivity to mycobacterial allergens, which persisted until the end of the experiment. Clinical and pathoanatomical manifestations of the disease were not observed in irradiated and intact animals.

The results of previous researchers in the area of studying the allergic reactivity and state of delayed hypersensitivity of irradiated and infected animals with tuberculosis convincingly prove that ionizing radiation affects the manifestation of tuberculin sensitivity, the course of tuberculosis infection, and autoimmune processes in the body. The works of B.A. Egorov, A.A. Kirstner [31]; P.A. Kartashov et al. [32; 33]; N.N. Klemparskaya et al. [34-39]; R.V. Petrov [40; 41]; A.Yu. Kassich [42] and other authors showed that the effect of ionizing radiation is not the same depending on the value of the radiation dose. One of the reasons for the manifestation of non-specific reactions may be autoallergisation of the body by the decay products of the tissues of the irradiated body, which is especially pronounced with radiation damage. When studying the specificity of allergic reactions in tuberculosis in irradiated animals, it was determined that the occurrence of pseudoallergic ("false") reactions depends on the level of autosensitisation of the body, which, in turn, depends on the total radiation dose received. Thus, researchers believe that the main role in the pathogenesis of radiation damage is played by activated oxygen metabolites – products of lipid peroxidation, which cause the development of autoimmune processes in the macroorganism. After radiation exposure, autosensitisation of the body occurs due to a violation of the antigenic specificity of proteins. The resulting autoantibodies have cytolytic activity. N.N. Klemparskaya et al. [43] believe that autoimmune reactions in the irradiated body proceed according to the type of auto-allergic processes, the side effect of which is the occurrence of non-specific (pseudoallergic) reactions to the administration of homologous and heterologous allergens. Therewith, if autoantibodies completely neutralise the products of cellular destruction, the pathological process with the development of large amounts of cytotoxic autoantibodies does not occur. With incomplete neutralisation of products, clinical signs of radiation damage develop. Some researchers believe that autoantibodies formed in the irradiated body are involved in increasing its radioresistance with single sublethal doses and with chronic low-dose radiation. It is also known that in irradiated animals that are not infected with pathogens of infectious diseases, due to autosensitisation by decay products of their own tissues, skin allergic reactions can occur to the administration of various non-specific stimuli [1; 4; 10; 12; 15]. The authors have suggested that this phenomenon can be used to differentiate pseudoallergic reactions in animals, in particular those kept in the zone of radioactive contamination. The conducted experiments proved that when using non-specific heterologous allergens at the same time with specific diagnosticums when conducting allergic studies for tuberculosis, it is possible to assert the specificity of allergic reactions to tuberculin and allergen from atypical mycobacteria and the degree of autosensitisation of the body. If skin reactions develop simultaneously to the administration of different allergens (PPD-tuberculin for mammals, poultry, an allergen from atypical mycobacteria, brucellin and mallein), then this refers to an autoallergic state of the body caused by non-specific (non-infectious) agents, in particular, the action of ionizing radiation.

CONCLUSIONS

The effect of irradiation on the allergic reactivity of laboratory animals experimentally infected with tuberculosis pathogens was determined.

1. 14-60 days after infection with tuberculosis pathogens *M. bovis, M. tuberculosis* and *M. avium*, 90-100% of laboratory animals developed allergic reactions to mammalian and poultry PPD-tuberculin, mainly to a homologous allergen. Allergic reactivity persisted until 90 days of the study.

2. After irradiation with sublethal doses of gamma rays, cavies developed non-specific reactions to tuberculin, mallein, and brucellin. In cavies not infected with the causative agent of tuberculosis, non-specific reactions to mycobacterial allergens were observed 7 days after gamma radiation exposure at a dose load of 200 R in 16.6%; 150 R – 5.3% in the group, and after 27 days in those irradiated with doses of 50 R and 100 R in 25% and 33% of the studied animals, respectively. Reactions manifested themselves in the form of infiltrates at the allergen injection site with necrosis in the centre and developed over time at the same time as specific tuberculin reactions.

3. Isolated reactions to brucellin and mallein occurred in animals infected with the causative agent of tuberculosis and intact animals 60 days after irradiation with doses of 50 R, 100 R and 150 R. The manifestation of non-specific allergies in irradiated laboratory animals depends on the radiation dose rate and radiosensitivity of the animals. Further studies of the allergic reactivity of farm animals exposed to tuberculosis are required.

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Вплив іонізуючої радіації на стан алергічної реактивності інфікованих туберкульозом лабораторних тварин

Володимир Юрійович Кассіч[1], Оксана Іванівна Касяненко[1], Володимир Володимирович Зажарський[2], Іван Володимирович Яценко[3], Жанна Євгеніївна Кліщова[4]

[1]Сумський національний аграрний університет
40000, вул. Г. Кондратьєва, 160, м. Суми, Україна

[2]Дніпровський державний аграрно-економічний університет
49000, вул. Сергія Єфремова, 25, м. Дніпро, Україна

[3]Харківська державна зооветеринарна академія
62341, вул. Академічна, 1, с. Мала Данилівка, Україна

[4]Медичний інститут Сумського державного університету
40000, вул. Санаторна, 31, м. Суми, Україна

Анотація. Алергічне дослідження з використанням ППД-туберкулінів є основним методом прижиттєвої діагностики туберкульозу сільськогосподарських тварин та птиці. Проте відомо про зниження діагностичної цінності алергічних реакцій після опромінення тварин, появу неспецифічних, псевдоалергічних реакцій. Однією з причин прояву неспецифічних реакцій може бути аутосенсибілізація (аутоалергізація) організму продуктами розпаду особистих тканин, що особливо виражено за променевого ураження. Іонізуюча радіація впливає на прояв туберкулінової чутливості, перебіг туберкульозу та аутоімунні процеси в організмі. Диференціальна діагностика неспецифічних туберкулінових реакцій лишається поки що не повністю вирішеною проблемою, хоча існує цілий ряд тестів для її здійснення. Після аварії на Чорнобильській АЕС на прилеглих забруднених радіоактивними речовинами територіях лишилося значне поголів'я тварин, у тому числі інфікованих збудником туберкульозу та атиповими мікобактеріями. Відомо, що радіаційне опромінення призводить до аутосенсибілізації організму продуктами розпаду власних тканин і розвитку неспецифічних псевдоалергічних реакцій на гетерологічні алергени. Тому була проведена робота з вивчення алергічної реактивності хворих на туберкульоз і сенсибілізованих атиповими мікобактеріями опромінених гамма-радіацією лабораторних тварин (200 морських свинок). Було встановлено, що через 14–60 діб після зараженням збудниками туберкульозу у 90–100 % мурчаків розвивались алергічні реакції на ППД-туберкулін для ссавців та птиці, переважно на гомологічний алерген. Алергічна реактивність зберігалась до 90 доби дослідження. Після опромінення сублетальними (не летальними) дозами гамма-променів у заражених та інтактних морських свинок розвивались неспецифічні реакції на туберкулін і гетерологічні алергени: малеїн та бруцелін. У незаражених збудником туберкульозу мурчаків через 7 діб після опромінення гамма-випромінюванням спостерігали неспецифічні реакції на мікобактеріальні алергени при дозовому навантаженні 200 Р у 16,6 %; 150 Р – 5,3 % по групі, а через 27 діб у опромінених дозами 50 Р та 100 Р у 25 % та 33 % досліджених тварин, відповідно. У інфікованих збудником туберкульозу та інтактних тварин через 60 діб після опромінення в дозах 50 Р, 100 Р та 150 Р виникали поодинокі реакції на бруцелін та малеїн. Прояв неспецифічної алергії у опромінених тварин залежала від потужності дози опромінення та радіочутливості тварин

Ключові слова: туберкулін, гетерологічні алергени, гамма-опромінення, мікобактерії, алергічні дослідження