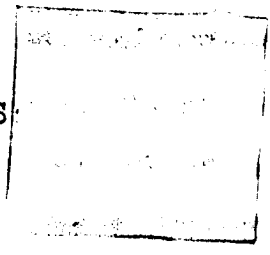


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DYNAMICS OF THE LEUKOCYTIC REACTIONS IN RABBITS
IN ACUTE RADIATION SICKNESS

By Ye. A. Dikovenko

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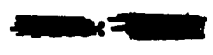
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DYNAMICS OF THE LEUKOCYtic REACTIONS
IN RABBITS IN ACUTE RADIATION SICKNESS

[Following is a translation of an article
by Ye. A. Dikovenko (Sukhumi) in Patolog.
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(From the Sukhumi Institute of Experimental
Pathology and Therapy of the Academy of Medical Sciences
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Data concerning the regulation of the blood system in irradiated animals are represented in the literature in an extremely incomplete fashion. Specifically, practically no investigation has been made of the blood reaction to various physiological stimuli used under conditions of radiation pathology. The work of Ye. I. Komarov (7) is an exception; here, a study was made of the leukocytic reactions to a food stimulus in male cats irradiated with X-rays in doses of 300, 600 and 1200 r. The author observed a marked distortion of the leukocytic reactions not only against the background of the radiation leukopenia but also during the period when there was still no leukopenia. In 1955-1956 we, in conjunction with our students B. V. Astrakhan and G. D. Monzul' (2), observed a change in the leukocytic reaction to milk in male cats irradiated with a dose of 500 r, which was most pronounced during the late period of the sickness (fourth to sixth week).

The present work was undertaken as the development of these observations. As a stimulus producing the reaction in the blood we utilized, just as we had before, the parenteral injection of milk.

It is known that the intramuscular administration of milk produces an increa

in the leukocyte count for three to four hours in healthy male cats and rabbits (3, 8, 10). This reaction served as a criterion of the state of regulation of the blood system ^{under} various experimental conditions. D. I. Goldberg and his coworkers (4) studied the leukocytic reaction to milk clinically, in various mental and somatic diseases in people.

Our communication is based on material obtained in 182 experiments on 45 rabbits. The animals were given three cubic centimeters intramuscularly (in a dose of 1.5 cubic centimeters into both thighs) of a boiled and filtered 10 percent solution of dry preserved milk. The leukocyte count was investigated for four hours at 30-minute to one-hour intervals; in the majority of experiments the differential count was also made. The investigation was conducted on a fasting stomach; the appearance and the odor of the food were also excluded.

It was first established on 37 healthy rabbits that the leukocytic reaction to milk was quite constant and well expressed in them. The increase in the leukocyte count occurred 30 minutes to two hours after the injection of milk; in half of the cases it was preceded by a brief leukopenic phase. The maximum increase in the leukocyte count during the experiment amounted to an average of 116 percent of the original level in the healthy animals. Four hours after the administration of milk the leukocyte count was close to the original or remained somewhat elevated. The leukocytosis occurs chiefly because of the increase in the granulocytes (segmented and stab pseudoeosinophils), with a relative lymphocytopenia, although the absolute lymphocyte count may increase somewhat. The erythrocyte count did not change essentially after the injection of milk.

Renewal of the milk injections in the same rabbits after five to ten days led to a well expressed reaction with a repetition six times. This made it possible for us, by adhering to the interval between the experiments indicated, to

investigate the same animals repeatedly before irradiation and at various times after it.

A total-body irradiation of 39 rabbits was performed on X-ray therapeutic RUM-5 apparatuses with the simultaneous operations of two apparatuses. The irradiation conditions were the following: 180 kv, current 15 ma, distance from the anode, 78 cm; filters 0.5 mm Cu and one mm Al; dose rate 18.5 r per minute; doses 300 and 600 r. The leukocytic reactions were investigated one, four, nine, 11, 16, 21, 30 and 35 days after the irradiation; each rabbit was investigated four to six times at intervals of five to eight days.

Irradiation with 600 r caused acute radiation sickness, which terminated on the 30th day with the death of approximately 50 percent of the animals. For the purpose of eliminating the general early reaction, which occurs very stormily in the rabbits and frequently terminates in death during the first few hours after irradiation with the use of large doses of radiation, anesthesia was used immediately after the irradiation--the production of a drowsy state with ether and the administration of one to 1.5 cubic centimeter of 10 percent sodium pentothal solution. The animals were maintained in a state of superficial sleep for two or three hours, because of which it was possible to lessen the severity of the early reaction to a considerable degree, although three rabbits still died from the X-ray shock. For the purpose of equalizing the conditions the control (non-irradiated) rabbits were anesthetized for the same time and investigated in parallel with the irradiated animals.

A day after the irradiation with 600 r during a period when a pronounced leukocytosis was observed in all the rabbits, the positive reaction to the injection of milk was maintained in four out of seven rabbits; in three animals the leukocyte count did not increase. The typical course of the leukocytic curve was altered in all the animals: following a brief increase or without it the leukocyte count decreased

rapidly, and four hours after the injection of milk amounted to 16.4 percent of the initial level, on the average (4800 as against 29,600). On the fourth day of radiation sickness the administration of milk produced a leukocytic reaction similar to the normal type but occurring at a reduced level. The leukocyte count increased from 2600 to 6500, on the average; in one case out of eight there was no positive reaction. On the ninth day after the irradiation the leukocytic reaction was also positive in seven out of eight animals; the leukocyte count increased from 4000 to 9200, on the average, and then dropped to the original level. On the 11th-17th day the reaction was negative or inverted (paradoxical) in all 18 rabbits investigated at this time. The injection of milk in the majority of cases led to a reduction in the leukocyte count (by comparison with the original). On the 11th day the leukocyte count decreased after the injection of milk from 4200 to 1400, on the average. On the 17th day the most marked reduction was observed in those cases where the radiation leukoepnia had already been replaced by restitution of the normal leukocyte count. Thus, in rabbit No 30 following the injection of milk the leukocyte count dropped from 8150 to 1900; in rabbit No 31, from 16,400 to 2150. In animals with a low original leukocyte count the injection of milk did not evoke any leukocytic reaction. On the 21st day of radiation sickness the positive reaction to milk was recovered in the majority of animals; however, in two out of nine rabbits it remained negative. Thirty days after the irradiation the injection of milk produced a typical leukocytosis in all the rabbits, even more pronounced than before the disease--an average increase in the leukocytes by 180 percent (38,080 as against 13,600 before the administration of milk). The results of the various experiments obtained are presented in their summarized form in the Table.

On the fourth to ninth day after the irradiation, with a positive reaction to milk, a pronounced increase in the absolute and relative granulocyte content occurred accompanied in almost all cases by an increase in the number of stab forms. The lymphocyte count did not change essentially. Therefore, the general rules and regulation of the change in the differential count were maintained, despite the different original background; whereas in the healthy rabbits lymphocytes predominate in the blood, in the irradiated animals a relative granulocytosis was observed with a relative and absolute lymphocytopenia.

During the period when an inverted leukopenic reaction occurred in response to the injection of milk (on the 11th-17th day of the sickness) the reduction occurred chiefly because of the reduction in the granulocyte count.

After a total-body irradiation with 300 r, which produces a mild form of radiation sickness in the rabbits, an absence of reaction to milk was observed at the same time as after a dose of 600r r, but it was noted in only three out of 12 animals. In the other cases, the dynamics of the leukocytic reactions did not show any

deviations from the normal. Apparently, the change in the reaction of the blood to an additional stimulus of protein nature depends on the severity of the radiation sickness, and the dose of 300 r approaches the threshold dose for rabbits in this respect.

Therefore, four periods may be distinguished in the change in the regulation of the hematopoietic system under the influence of large doses of ionizing radiation.

On the first day after irradiation, that is, during the period of the generally early reaction when leukocytosis is observed in the peripheral blood, the reaction to the milk injection is altered--after a brief increase in the leukocyte count (or without it) the count decreases sharply and afterwards remains at a low level. In the

irradiated animals which were not given milk the post-radiation leukocytosis was maintained for a longer time. The impression is created that the parenteral administration of milk on the first day after irradiation accelerates the development of radiation leukopenia.

In the second period (third to 10th day) the injection of an additional stimulus of protein nature into the body produces a more or less normal type leukocytic reaction, despite the marked leukopenia. Under the influence of the milk the leukocyte count increases by 3000-5000 in two or three hours, after which it drops to the original level. During this period, despite the considerable depression in hematopoiesis, an adequate reaction is maintained to the protein stimulus by the blood system.

In the third period (10th-20th day of the sickness), at which time the leukocyte count in the peripheral blood begins to increase gradually, the reaction to the protein stimulus is absent or assumes a paradoxical nature.

In the fourth period (21st-30th day) the positive reaction to milk is restored; in its strength it exceeds the reaction observed in the animals before the irradiation.

These data show that there is a definite difference between the intensity of hematopoiesis and the functional capacity of the organism for reacting to the protein stimulus with leukocytosis.

In recent years progressively more facts are being accumulated which confirm the fact that leukocytic reactions occur with the participation of the hematopoietic apparatus and are associated with an increased production of mature elements of the granulocytic series from the bone marrow (4,5 and others). M.D. Shkol'nikova showed that leukocytosis was observed following the injection of a BCG culture not only in the peripheral blood vessels but also in the blood vessels of the internal organs and was associated with changes in the myelogram attesting to an increase in granulocytogenesis (11). An increase was noted in the bone-marrow

hematopoiesis following the parenteral injection of milk (1). We observed an increase in the protein and nucleoprotein metabolism of the bone marrow under the influence of milk and other agents producing a leukocytic reaction.

Therefore, an increase in the leukocyte count in response to stimulation is not only an index of the state of regulation of the blood but also to some degree reflects the functional possibilities of the bone marrow, which do not always coincide with the original condition of hematopoiesis.

The existence of an adequate leukocytic reaction in the first week after irradiation shows that despite the marked depression of hematopoiesis a more or less normal regulation of the blood system is maintained in the irradiated organism up to a certain period, and there are certain functional reserves which assure a temporary increase in the leukocyte count.

In the literature there is information to the effect that the combination of radiation injury and a wound (9) as well as of irradiation and infection (5) in certain cases delays the development of radiation leukopenia and reduces the degree of it. The repeated administration of killed microbial cultures into irradiated rabbits exerted a certain stimulating effect on hematopoiesis (6). Our results are in agreement with these data and indicate the expediency of using hematopoietic stimuli in the early periods after irradiation.

A disturbance in the leukocytic reactions during the period of incipient recovery of hematopoiesis is apparently conditioned, by and large, by the change in the normal regulation of the blood system, because the bone marrow at this time contains a considerable number of hematopoietic elements. The mechanism of disturbance of this regulation needs further study.

Leukocytic Reaction to Milk in Rabbits Irradiated
With 600 r

Rabbit #	Before ir- radiation	Day after irradiation						Outcome of sickness	
		1-R	4-R	9-R	11-R	17-R	21-R		31-R
1	+	-			-		-	+	survived
3	++		+			-			did on 18th day
4	++		-						> > 11th >
5	+++	-		+		-	+	+	survived
7	+++	-		+		-	+	+	>
12	+++	-							did on 2nd day
13	+++	-		+					> > 10th >
14	+++		+	-					> > 11th >
16	+++		+		-		+	+	survived
17	+++		+		-		+	+	>
18	+++	-		+		-	+	+	>
19	+++	-		+			+	+	>
20	+++	-			-				did on 13th day
21	+++		+		-				> > 14th >
22	+++		+		-				> > 18th >
23	+++			+		-			survived
24	+++		+		-		+	+	>
28	+++				-		-	+	>
29	+++				-			+	did on 18th day
33	+				-				>
No. of in-vestigations	21	7	8	8	9	9	9	9	

Conclusions

1. Radiation sickness which occurs in rabbits following a total-body irradiation with X-rays in a dose of 600 r, is associated with a change in the regulation of the blood system, which is of a wave-form character.

2. The leukocytic reaction to the parenteral injection of milk is inverted on the ~~first~~ first day after irradiation, recovered on the third to 10th day, becomes paradoxical or is absent from the 10th to the 20th day and is again recovered, exceeding the normal by the 21st to 30th day.

3. A disturbance in the regulation of the blood system does not coincide in time with the disturbance in the hematopoietic function. During the period of marked depression of hematopoiesis a parenterally injected protein stimulus produces a temporary increase in the leukocyte count. The paradoxical reaction is most pronounced during the period of incipient regeneration of ^{the} hematopoietic tissue.

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