CHANGES IN THE PHAGOCYTIC REACTION AND IN ORGANS OF THE RETICULO – ENDOTHELIAL SYSTEM IN ALBINO MICE FOLLOWING ADMINISTRATION OF TETRACYCLINE

(UDC 615.779.931-092.259:[612.112.2+612.429)

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 61, No. 2,
pp. 72-75, February, 1966
Original article submitted July 13, 1964

In spite of its great importance, the problem of the effect of antibiotics on the defense reaction of the organism has not been completely solved. Contradictory opinions on this subject have been expressed in literature[1-8,11].

Because the phagocytic reaction is one of the indices of the defense mechanism of the organism, it was our purpose to study the effect of tetracycline on phagocytic reaction and on the organs of the reticulo–endothelial system (liver, spleen, lymph nodes, bone marrow) and on other organs in animals to which tetracycline was administered.

METHODS

The first 4 series of experiments (10 animals per series) were conducted on male albino mice weighing 20-22 grams. They were fed bread, oats, milk, carrots, and chalk. Prior to experiments, all the animals were kept for a week under identical conditions. Then for a period of 10 days they were fed tetracycline once a day in doses of 10 mg/kg (series I), 50 mg/kg (series II), and 500 mg/kg (series III). The control group (series IV) did not receive the antibiotic.

The doses used by us were those mentioned in literature [9,10]. A dose of 10 mg/kg is regarded as low, that of 50 mg/kg as mean therapeutic, and 500 mg/kg as toxic for white mice weighing 18-20 g. The phagocytic reaction was studied in the abdominal exudate of mice. To produce the exudate, mice were injected intraperitoneally with 2 ml of sterile meat-peptone broth, and, after 2 h, also intraperitoneally, with a suspension of a 24-h agar culture of strain No. 209 Staphylococcus consisting of 2 billion microbial cells per 1 ml. 30 min, 3, 6, 24, 48, and 96 h after injection of the bacteria, exudate was removed from the abdominal cavity by means of a sterile syringe. Smears were made of the exudate and were fixed in Nikiforov's mixture and stained with Giemsa. The number of phagocytized bacteria in 100 leucocytes were counted, the phagocytic index was determined and the percentage of phagocytizing leucocytes was calculated.

In order to determine the phagocytic activity of leucocytes of peripheral blood in vitro, we used 16 rabbits which were not given tetracycline. 0.05 ml of a 2% sodium citrate solution were placed in a test tube to which was added a drop of blood of the experimental animal and a drop of a suspension of a 24-h agar culture of strain 209 Staphylococcus containing 2 billion microbial cells per 1 ml and a drop of tetracycline solution (1, 10, and 50 units per drop). The tubes were incubated at 37° C. for 30 min. Smears were made of the mixture. These were stained in the same manner as above.

RESULTS

The results of our studies on the phagocytic activity of leucocytes in the peritoneal exudate and in peripheral blood are presented in Tables 1 and 2.

TABLE 1. Effect of Tetracycline on Phagocytosis in vivo in Mice (mean values)

Experimental series	Dose of tetracycline (mg/kg)	Time of exposure	Experimental		Control	
			Percentage of phagocytizing leucocytes	Phagocytic index	Percentage of phagocytizing leucocytes	Phagocytic index
I	10	30 min	67	2.8	64	1.65
		3 h	62	1.6	57	1.2
		6 h	41	1.8	29	0.7
		24 h	38	0.9	25	0.4
		48 h	27	0.6	32	0.5
		96 h	34	0.8	29	0.7
II	50	30 min	68	3.9	62	1.72
		3 h	46	1.4	48	1.16
		6 h	39	1.19	26	0.62
		24 h	38	0.84	20	0.37
		48 h	26	0.58	30	0.42
		96 h	42	0.88	34	0.54
III	500	30 min	51	1.2	65	1.6
		3 h	47	0.9	56	1.3
		6 h	21	0.7	30	0.8
		24 h	18	0.5	27	0.5
		48 h	15	0.4	31	0.6
		96 h	17	0.6	29	0.8

TABLE 2. Effect of Tetracycline on Phagocytosis in vitro in Rabbits (mean values)

Dose of tetracycline (in units)	Experiment		Control	
	Percentage of phagocytizing leucocytes	Phagocytic index	Percentage of phagocytizing leucocytes	Phagocytic index
1	24	0.4		
10	26	0.88	20	0.53
50	31	1.5		

It will be seen in Table 1 that the data obtained on in vivo phagocytic reaction could not be used to make a conclusion regarding a stimulating effect of tetracycline on phagocytosis. The phagocytic indices in the experiments and the controls were almost identical. A certain difference was found only in animals which received tetracycline in doses of 50 mg/kg and from which the exudate was obtained after 30 min. At later periods, the phagocytized bacteria were destroyed, which led to a lowering of the phagocytic index in experiments as well as in controls.

In in vitro experiments, the effect of tetracycline on the phagocytic reaction was more clearly defined and was determined, as seen in Table 2, by the dose of tetracycline. Thus, when one unit of tetracycline was added to the suspension of bacteria and leucocytes, the phagocytic index in the experiments was almost the same as that in the controls. The addition of 10 units of tetracycline led to an increase of the phagocytic index in the experiment as compared with that of the control to the extent of approximately 50%. When 50 units of tetracycline were added to the bacteria and leucocytes, the phagocytic activity became almost three times that of the control.

Because we could not detect any stimulation of phagocytosis by tetracycline in vivo, while in vitro the stimulation was clear and was determined by the dose of the antibiotic, it could be supposed that tetracycline exerts a lesser effect on leucocytes than on bacteria. Apparently, the antibiotic alters the metabolism of microbial cells and thus raises the phagocytic activity of leucocytes.

The results of study of histomorphological changes in organs of the reticulo–endothelial system of animals receiving tetracycline in the same doses as in the preceding experimental series, but for longer periods (10-60 days),

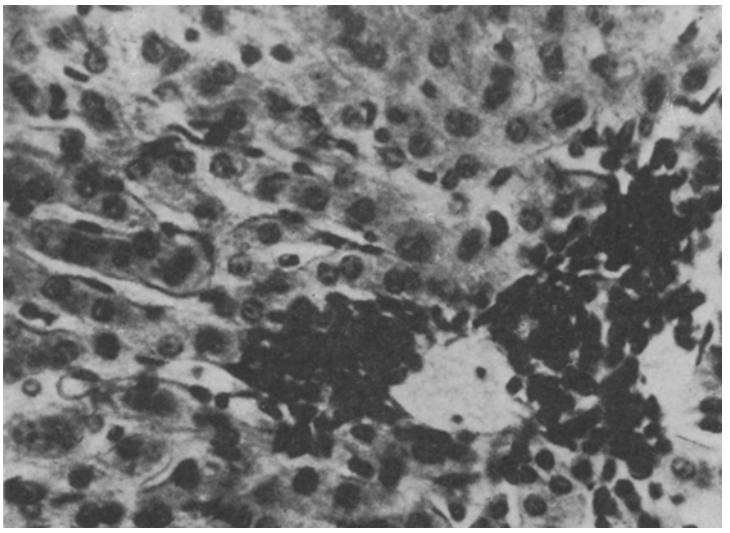

Fig. 1. Focal perivascular lymphoid histiocytic reaction in the liver. Hematoxylin-eosin. Obj. 40×, oc. 7×.

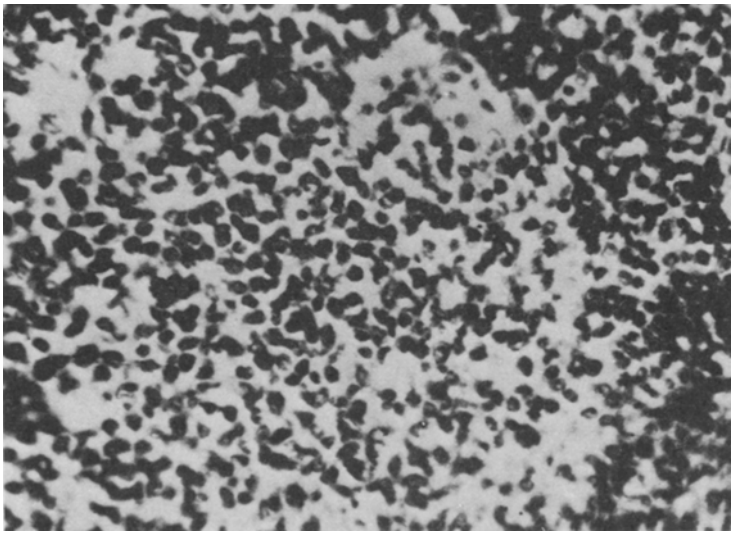

Fig. 2. Hyperplasia of lymphoid cells in the centers of spleen follicles. Obj. 8×, oc. 10×.

have established the following. Microscopic examination of mesenteric lymph nodes and of inguinal lymph nodes of mice which received tetracycline in a dose of 10 mg/kg has shown a moderate hyperplasia of lymphoid-reticular cells; in the spleen a hyperplasia of follicles and of the medulla; in the liver a formation of proliferates around mainly large blood vessels, consisting of lymphoid and adventitial cells (Fig. 1). There were no apparent changes in the argyrophilic fibers in lymph nodes, spleen and liver.

When mice were given tetracycline in a dose of 50 mg/kg, there was considerable plethora, increase in the size of the spleen and mesenteric lymph nodes. The weight of the lymph nodes reached 12-20 mg. Microscopic examination of lymph nodes, spleen, bone marrow, and liver has revealed a more defined, as compared with the previous experimental series, hyperplasia of lymphoid (Fig. 2), reticular and endothelial cells of the sinuses. This was accompanied by a hyperplasia of argyrophilic fibers in the spleen and liver.

In mice which received tetracycline in a dose of 500 mg/kg, in addition to hyperplastic processes there were also dystrophic changes in lymphatic tissues. In some cases, hyperplastic phenomena were very widespread and lymphoid-histiocytic infiltrates were seen in the myocardium and in other organs. In the liver, there was a moderate adiposis of cells in the periphery of lobules, and granular dystrophy.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
