THE EFFECT OF PENICILLIN ON THE BLOOD SYSTEM

COMMUNICATION II. THE CHARACTER OF THE LEUCOCYTE REACTIONS IN ANIMALS DURING PROLONGED ADMINISTRATION OF PENICILLIN

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As our investigations have shown, penicillin, when administered to healthy persons and animals, produces no essential changes in the peripheral blood but in a number of cases it accelerates the maturation of eosinophils in the bone marrow. In addition, reports in the literature and our own personal experience clearly indicate a comparatively high incidence of eosinophilia during penicillin therapy. In this connection we decided to study the character of the leucocyte reactions to various stimuli during the prolonged administration of penicillin. As suitable stimuli we used the intramuscular injection of 3 ml of skimmed milk. According to N. I. Veshchezerov, R. I. Volynskaia and A. Ia. Iaroshevskii [1, 2, 3], in cats the injection of milk always causes a pronounced neutrophilic leucocytosis with a marked shift in the leucocytic formula to the left. Another stimulus was distension of the stomach of cats through a fistula; it is well known at the present time that this type of manipulation leads, after a transient leucopenia, to leucocytosis without any marked changes in the leucocytic formula. Thus, the use of the first stimulus combined both nervous and humoral factors, whereas stretching of the mechanoreceptors of the stomach is an example of reflex action.

EXPERIMENTAL METHOD

At the beginning of the experiments the leucocyte reaction to the intramuscular injection of milk or to stimulation of the stomach was studied on two occasions in two weeks; during the next 14-28 days an injection of 50,000 units of penicillin was given every 4 hours, and the stimuli were repeated on the 7th-9th-14th and 27th days of administration, and also a week after the injections had been discontinued. Blood was taken from the ear of the animals before stimulation and 30 minutes, 1, 2, 3 and 4 hours after stimulation.

Althogether 78 experiments were carried out on 12 cats (in four of these animals a gastric fistula was created 3 months beforehand).

EXPERIMENTAL RESULTS

In 6 our of 8 animals, in response to the injection of 3 ml of milk a marked leucocytosis was observed, appearing usually after a transient ($\frac{1}{2}$ -1 hour) leucopenia. The maximum increase in the white cell count took place in the 2nd and 3rd hours of the experiment. After only 2 hours a marked shift was observed in the leucocytic formula with an increase in the content of stab cell forms to 9-16%.

The content of eosinophils under these circumstances was essentially unchanged (Fig. 1, a and b and Fig. 2). It can be seen from the Table that in two experiments (November 13 and 26) carried out before administration of

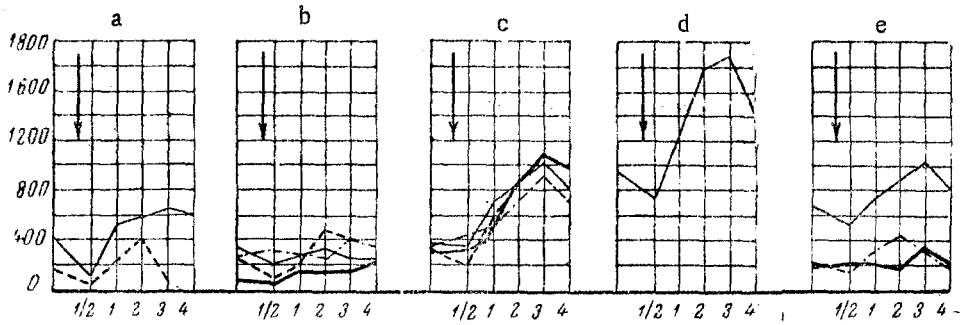

Fig. 1. Changes in the numberof eosinophils during penicillin administration after injection of milk.
a, b) Before giving penicillin; c) on the 2nd day of penicillin administration; d) on the 7th day of penicillin administration; e) 9 days after discontinuing penicillin. The arrows indicate injection of milk.

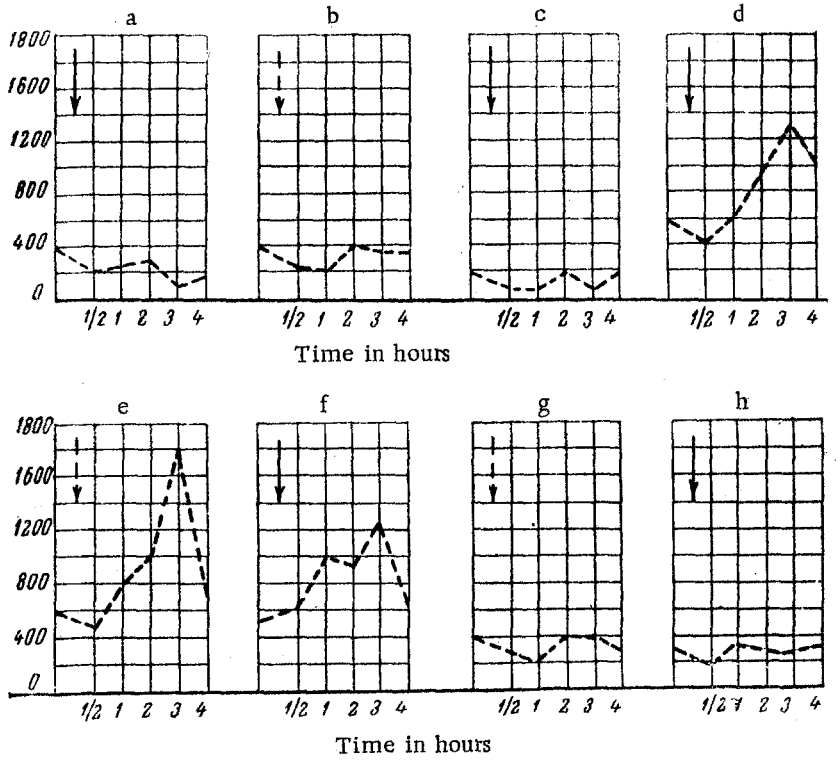

Fig. 2. Changes in the eosinophil content after injection of milk and distension of the stomach.
a, b, c) Before injection of penicillin; d) on the 10th day after injection of penicillin; e) on the 16th day; f) on the 28th day of penicillin administration; g-h) on the 8th-9th days after discontinuing penicillin; ↓ – injection of milk; ⇣ – distension of stomach.

penicillin, during investigation of the blood a shift of the leucocytic formula to the left, without any notable increase in the eosinophil content, was clearly observed in response to the injection of milk. After preliminary injections of penicillin (see Table – experiments on December 10 and 28, Fig. 1, c and d and Fig. 2), on the 2nd and 7th days the injection of milk leads to a sharp increase in the eosinophil content; 9 days after discontinuing

TABLE

Changes in the Character of the Leucocyte Reactions to Milk After Administration of Penicillin. Experiment Dated November 13, 1953

Time in hr and min	Hemoglobin (in %)	Red cells	White cells	Eosinophils	Stab cells	Segmented neutrophils	Lympho-cytes	Monocytes	Absolute eosinophil count
Before administration of penicillin									
12^{15}	59	4 440 000	15 100	2,5	4	70	18	5,5	377,5
12^{21}	2.5 ml of milk injection intramuscularly								
12^{51}	60	4 580 000	8 200	2	4	72	12	10	164
13^{21}	59	4 490 000	16 200	1,5	12	69,8	12,0	5	243
14^{21}	58	4 570 000	21 900	1,5	14,5	65	13	6	328,5
15^{21}	59	4 840 000	19 100	0,5	10,5	69,5	13,5	6	95
16^{21}	60	4 950 000	15 400	1	7	71	14,5	6,5	154
Experiment dated November 26, 1953									
12^{01}	59	4 300 000	13 100	1,5	4	71,5	17,5	5,5	196,5
12^{12}	2.5 ml of milk injected intramuscularly								
12^{42}	61	4 540 000	9 600	1	4	74,5	16	4,5	96
13^{12}	62	1 490 000	13 700	0,5	4,5	78,5	12	4,5	68,5
14^{12}	61	4 430 000	19 950	1	10	76	9,5	3,5	199,5
15^{12}	60	4 470 000	14 260	0,5	12	74,5	8,5	4,5	71,3
16^{12}	61	4 510 000	14 100	1,5	12,5	71	12,5	2,5	211,5
Experiment dated December 10, 1953. On the 9th day of penicillin administration									
12^{03}	59	4 500 000	15 200	2	3,5	67,5	20,5	6,5	304
12^{10}	2.5 ml of milk injected								
12^{40}	62	4 940 000	11 200	4	3	66,5	19,5	7	448
13^{10}	60	4 750 000	11 350	5	4,5	66,5	17,5	6,5	567,5
14^{10}	61	4 750 000	18 500	5	6	71	12	6	925
15^{10}	62	4 860 000	21 900	6	10	66	11,5	6,5	1 314
16^{10}	59	4 520 000	17 000	6	10	67,5	10,5	6	1 020
Experiment dated December 28, 1953. On the 27th day of penicillin administration									
12^{16}	56	4 370 000	15 400	3,5	4	69,5	17,5	5,5	539
12^{21}	2.5 ml of milk injected into the paw.								
12^{51}	57	4 470 000	13 900	4,5	3,5	69,5	16,5	6	625,5
13^{21}	58	4 560 000	15 100	6,5	6	65,5	15,5	6,5	981,5
14^{21}	58	4 600 000	15 270	6	8,5	62,5	15,5	7,5	916,2
15^{21}	60	4 720 000	18 900	6,5	11	60	17,5	5	1228,5
16^{21}	59	4 620 000	16 100	4	10,5	67	13	5,5	644

the injections of the antibiotic the reaction to milk once more returns closer to its original pattern (Fig. 1, e). In order to avoid the influence of the repeated injections of a foreign protein themselves, in two cases we injected milk from an animal receiving penicillin for 2 weeks without preliminary injection of milk, and in this case too eosinophilia was observed.

Analogous findings were obtained also in experiments in which the stomach was distended by means of a thin-walled rubber balloon inserted within its lumen (Fig. 2 and 3); the pressure inside it was usually 35-40 mm of mercury. In Fig. 3 it may be seen that on the 15th and 22nd days of administration of penicillin, stumulation of the mechanoreceptors of the stomach leads to a significant eosinophilia, disappearing on the 9th-10th day after discontinuing the injection of the antibiotic.

The results of our experiments show that penicillin causes a state of sensitization in which the ordinary leucocyte reactions to humoral and reflex stimulation are modified and acquire the character of eosinophilia.

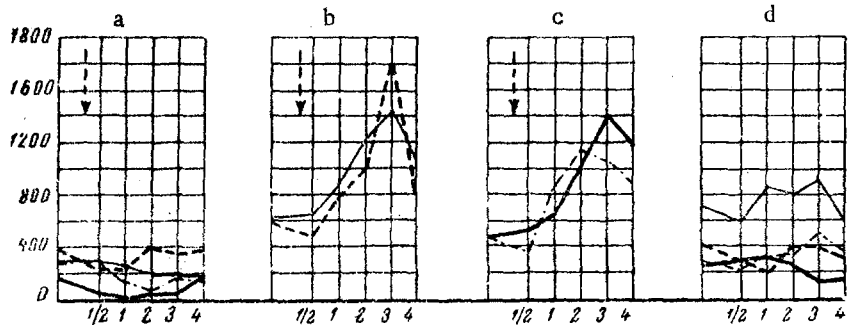

Fig. 3. Changes in the eosinophil content after distension of the stomach. a) Before administration of penicillin; b) on the 15th day of administration of penicillin; c) on the 22nd day of administration of penicillin; d) on the 9th-10th day after discontinuing penicillin.

Thus, in those cases in which the animals (cats) were given preliminary injections of penicillin, an injection of foreign protein in the form of milk causes eosinophilia instead of the usual neutrophilic leucocytosis.

Stimulation of the mechanoreceptors of the stomach in cats receiving injections of penicillin also leads to an increase in the number of eosinophils in the peripheral blood.

SUMMARY

In response to milk injection or to stomach inflation leukocytosis develops in cats following a short period of leukopenia. There is also a shift of the leukocytic formula with an increase of the number of band forms without any rise in the number of eosinophilic elements. Preliminary administration of penicillin, injection of foreign protein (milk) or the stimulation of the gastric mechanoceptors caused a pronounced eosinophilia disappearing in 9-10 days after discontinuing the administration of this antibiotic. Thus, penicillin causes a condition of sensitization in which the usual leukocytic reactions to humoral and the reflex stimulations are distorted and acquire the character of eosinophilia.

LITERATURE CITED

[1] N. I. Veshchezerov, The Mechanisms of Pathological Reactions, 3, pp. 34-40, Leningrad (1941).*

[2] R. I. Volynskaia, The Mechanism of Leucocytosis, Dissertation, Leningrad (1946).*

[3] A. Ia. Iaroshevskii, Interoceptors of the Bone Marrow and Interoceptive Influences on the State of the Blood. Dissertation, Leningrad (1948).*

* In Russian.