

THE EFFECT OF PENICILLIN ON THE BLOOD SYSTEM

THE EFFECT OF PENICILLIN ON THE COMPOSITION OF THE PERIPHERAL BLOOD AND BONE MARROW IN MAN AND ANIMALS IN NORMAL HEALTH

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The introduction and widespread use of antibiotics in clinical practice has called for careful investigation of changes which may arise in various systems and organs. This investigation showed that in certain cases phenomena may be observed which must be assessed as side effects in relation to the therapeutic value of the antibiotics.

Changes in the blood system by the action of antibiotics have been studied by several workers, but their findings show considerable disagreement [2,3,5]. In individual cases, antibiotics may even cause an aplastic condition of the bone marrow [6,7]; so far as penicillin is concerned the majority of workers mention only the development of eosinophilia [1,4] in patients receiving this preparation. The mode of production of this eosinophilia has not yet been fully explained, since the problem of the action of penicillin on the blood system of man and animals in normal health has not yet been adequately studied. Such a study would enable a number of doubtful problems concerning the mechanism of development of these changes to be cleared up, since in this case the effect of penicillin would be studied without the ever present effects of the disease itself.

We studied the changes in the composition of the peripheral blood in 10 healthy human subjects and 18 animals (10 rabbits and 8 cats). In the 8 cats, in addition to the peripheral blood bone marrow hemopoiesis was also studied.

EXPERIMENTAL METHODS

Penicillin was injected every 3 hours, in a daily dose of 320,000 to 800,000 units, into persons prepared for plastic operations. The injections lasted for 7 to 35 days. The blood was examined 2-3 times before and 4 times during penicillin therapy. Hemoglobin estimation, erythrocyte and leucocyte counts and the leucocytic formula were determined; films were stained by the Romanowsky-Giemsa method, counting 400 cells.

Analogous investigations were made on 10 rabbits and 8 cats. Penicillin was injected intramuscularly in a dose of 50,000 units every 4 hours (300,000 units daily). The total dose of the antibiotic in the course varied between 2,100,000 and 18,600,000 units. Blood was taken from an incision in the ear one hour after injection of penicillin, in turn; besides estimation of the hemoglobin, erythrocytes, leucocytes and leucocytic formula, the reticulocyte count was also determined in the blood of the rabbits. In addition to the study of the effect of prolonged administration of the antibiotic, changes in the composition of the blood of cats arising during the 3 hours following injection were investigated. As a basis for comparison the initial state of the blood was

examined for 2-3 weeks before the experiments (usually every other day).

EXPERIMENTAL RESULTS

The human subjects were carefully examined before penicillin therapy, and none of them showed any inflammatory condition, raised temperature or deviation of their initial blood composition from normal.

The table shows the average results of the changes in hemoglobin content and in the erythrocyte count before and after penicillin treatment in all the subjects.

Changes in the Hemoglobin Content (Sahli) and the Erythrocyte Count in Human Subjects due to Penicillin, in 1 mm³

Subject	Before penicillin admin.		Completion penicillin admin.	
	Hemo-globin	Erythrocytes	Hemoglobin	Erythrocytes
M-ya	78	4 300 000	75	4 500 000
Ch-a	62	3 800 000	65	4 000 000
Sh	75	4 160 000	76	3 950 000
S-a	82	4 200 000	77	4 520 000
F-a	63	3 580 000	68	4 200 000
P-a	68	3 800 000	66	3 900 000
K-r	72	4 800 000	76	4 700 000
Kh-a	73	4 550 000	70	4 600 000
Z-ch	76	4 280 000	70	4 140 000
D-a	65	3 960 000	69	4 000 000

The table shows that no significant changes occurred in the hemoglobin content and erythrocyte count. Slight changes occurred in the leucocyte count; thus in 5 persons it increased (at the most by 3000 per 1 mm³), in 4 it was unchanged and in only one did it fall on the 4th day of penicillin administration to 2800 per 1 mm³, however on the 7th day it had risen to 6400. Regarding the eosinophilia observed in some patients, we paid great attention to determining the number of eosinophils; However, we did not obtain any convincing results. In 8 out of the 10 subjects the eosinophil content did not exceed 3%, and in only one of them did we find a brief (for one day) rise in the eosinophil content to 9% subsequently falling to 2%; finally, in the last subject it fell from 4 to 1-3%. Calculation of the absolute value of eosinophils did not introduce any appreciable correction to the results obtained. Thus, in all the subjects penicillin administration produced no appreciable change in the composition of the peripheral blood.

The rabbit experiments showed that prolonged administration of antibiotics produced no appreciable change in the composition of the blood of the animals. Thus, variations in the leucocyte count between 6000 and 10,000 per 1 mm³ did not exceed arbitrary limits. The same result was obtained with the cats. The hemoglobin content varied little, and in no case more than it did before administration of the antibiotic (within limits of 10-12 Sahli units).

The results of the reticulocyte counts, shown in Fig. 1, indicate that the changes in this index were irregular. It is true that in 4 rabbits there was some degree of reticulocytosis (from 0.6 to 3.2%), but these variations do not transgress the normally accepted limits.

Figure 1 illustrates the changes in the content of eosinophils (the estimation of eosinophils in rabbits is made difficult by the presence of pseudo-eosinophils, but it is perfectly possible). It was shown that in 6 animals, the number of eosinophils varied during the period of penicillin administration between 0-124 cells per 1 mm³ (expressed in absolute figures). In 3 rabbits a rise in this figure to 204 cells was noted on the 9th

day of administration, and in 1-196 on the 32nd day of penicillin administration. Expressed as percentages, these variations were from 0-2%. No changes were found in the other components of the leucocytic formula.

Quite similar results were obtained from the cat experiments. Investigation of the "acute" changes, i. e. those occurring within 3 hours of the injections showed constantly an increase in the leucocyte count (within limits of 3000-6000 cells per 1 mm³) which appeared only during the first hour. Variations in the eosinophil content were slight, within limits of 0-4%.

Since the blood changes in the healthy human subjects and animals caused by penicillin were insignificant, whereas clinical experience, including our own investigations, speaks of the development of eosinophilia in some such cases, we studied the state of bone marrow hemopoiesis in 8 animals (cats). Bone marrow was obtained by puncture of the distal epiphysis of the femur of these animals; besides studying the usual myelogram we also investigated the course of maturation of the eosinophils, making it possible to judge the effect of penicillin on eosinophilic growth in the bone marrow.

Analysis of the myelograms showed a tendency towards an increased content of erythroblasts, which led to a small reduction in the relation of leucoblastic and erythroblastic growth (Fig. 2). The observed in-

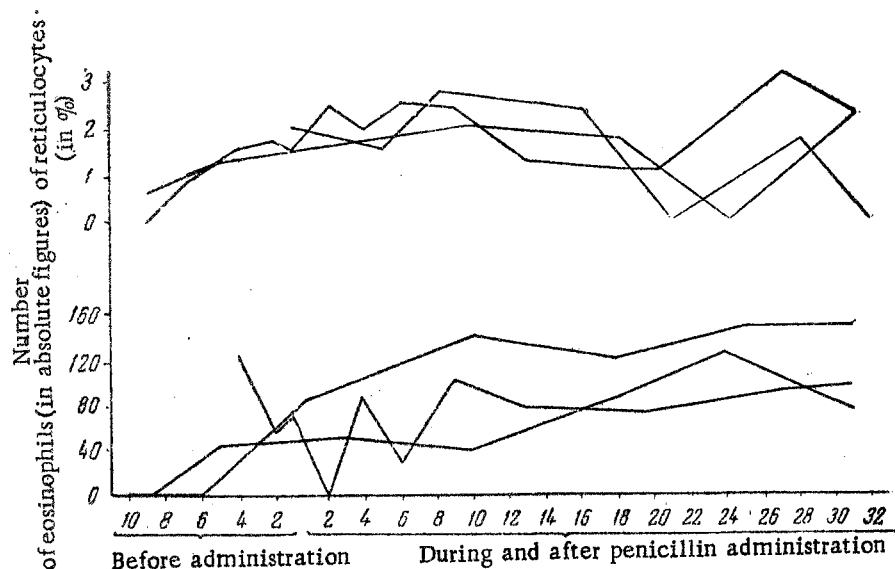


Fig. 1. Changes in the eosinophil and reticulocyte counts of rabbits with administration of penicillin.

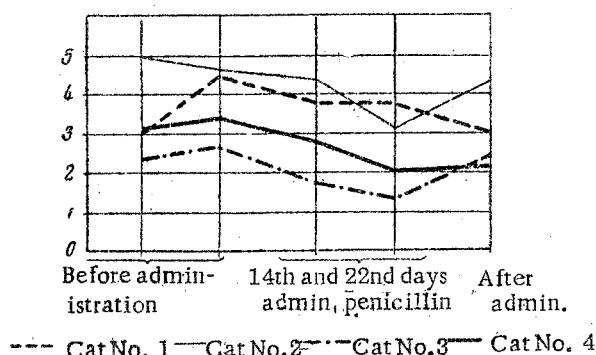


Fig. 2. Changes in the relation between leucoblastic and erythroblastic growth with administration of penicillin to cats.

crease in the number of erythroblasts affected all forms, but mainly the oxyphils. In Fig. 3 are shown changes in the maturation curve and the number of eosinophils in the bone marrow arising as a result of penicillin. These were most clearly shown in cat No. 4 in which there was a sharp increase in the content of more mature forms (eosinophilic metamyelocytes and polymorphonuclear cells). In two other animals similar changes were found, but to a lesser degree. In cat No. 1 there was a rise in the number of eosinophilic myelocytes and a fall in the content of more mature forms. Discontinuation of the penicillin in all cases led to restoration of the original relationship within 7-9 days.

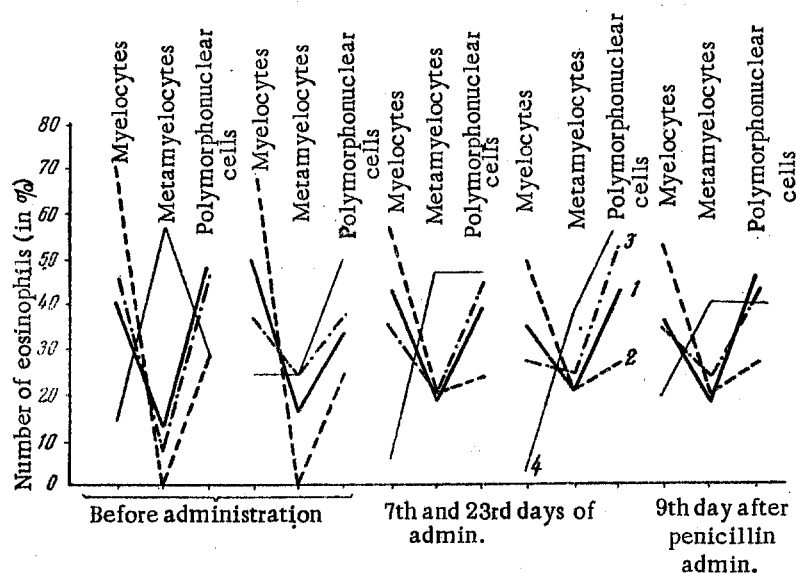


Fig. 3. Maturation of eosinophils with administration of penicillin to cats (1, 2, 3, 4).

SUMMARY

No marked changes have been noted in the peripheral blood of healthy humans injected with penicillin for 1-5 weeks. The same effect was noted in rabbits and cats. Some increase in the number of reticulocytes did not exceed normal values. Studies of bone marrow hemopoiesis have revealed a tendency to an increased number of erythroblasts, mainly of the oxyphilic group, and a rise in the number of eosinophils with their more early maturation. No such phenomena were noted in the peripheral blood. With cessation of penicillin injections initial states were restored in all cases.

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