

# EFFECT OF OROTIC ACID ON DEVELOPMENT OF ERYTHROCYTES AND GRANULOCYTES IN THE BONE MARROW

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Reports in the literature of the therapeutic effect of orotic acid in the anemias are highly contradictory. Most investigators [2, 5-8, 10, 12-15] report that this acid has a beneficial effect on hemopoiesis in anemias mainly of the megaloblastic type. Other authors [3-5, 11], however, obtained no effect from the use of orotic acid for the treatment of megaloblastic anemias.

The conflicting reports of the effect of orotic acid on hemopoiesis and on the composition of the peripheral blood in normal and pathological conditions have restricted the field of potential application of this substance.

In the present investigation, the action of orotic acid was studied on the peripheral blood and on the development of erythrocytes and granulocytes in the bone marrow of healthy animals.

## EXPERIMENTAL METHOD

Investigations were carried out on 27 male guinea pigs weighing 350 g and 22 male rats weighting 200 g. The guinea pigs were subdivided into three groups. Group 1 was the control. The experimental animals of groups 2 and 3 received orotic acid by mouth for 15 days in a daily dose of 100 mg/kg body weight (group 2) and 5 mg/kg body weight (group 3). The hemoglobin concentration, the erythrocyte, reticulocyte, and leukocyte counts and the leukocyte formula were determined for all the animals in the initial state. After administration of orotic acid for 15 days, the animals were again investigated and then killed. The marrow was taken from the sternum. The bone marrow films were dried, fixed with methanol and stained by the Giemsa-Romanovsky method. Between 300 and 400 cells were counted from each of the two series in the bone marrow: erythropoietic (proerythroblasts, erythroblasts, reticulocytes, erythrocytes) and granulopoietic (myeloblasts, promyelocytes, myelocytes, metamyelocytes, stab cells, and polymorphonuclear neutrophils).

The rats were divided into two groups (control and experimental). The experimental animals received orotic acid by mouth for 15 days in a daily dose of 100 mg/kg body weight. The subsequent investigations were carried out exactly as for the guinea pigs.

The numerical results were subjected to statistical analysis.

## EXPERIMENTAL RESULTS

The results of the investigation of the peripheral blood of both guinea pigs and rats showed that after administration of orotic acid for 15 days the erythrocyte and leukocyte counts and the hemoglobin concentration in the peripheral blood of the experimental animals of groups 1 and 2 remained within the limits of normal physiological variation.

No significant differences were likewise observed between the leukocyte formulas of the experimental and control animals.

A noteworthy feature was the increase in the number of reticulocytes in the peripheral blood of the experimental animals, especially in those receiving large doses of orotic acid (see figure).

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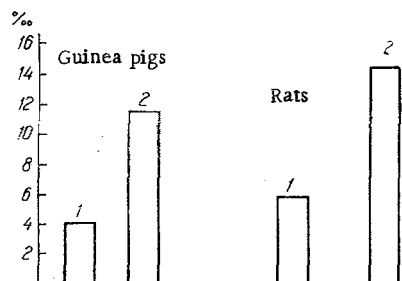


Fig. 1. Reticulocyte count in peripheral blood of experimental animals before and after receiving orotic acid (100 mg/kg). 1) Initial level; 2) after administration of orotic acid.

Table 1. Erythrocyte and Polymorphonuclear Neutrophil Counts in Bone Marrow of Guinea Pigs (in %;  $M \pm m$ )

Group of animals	Erythrocytes	P	Polymorphonuclear neutrophils	P
Control	45,5 ± 4,4		17,2 ± 3,3	
Experimental	69,3 ± 2,8	0,001	33,3 ± 2,7	0,01

Large doses of orotic acid had some effect on bone marrow function. A statistically significant increase in the number of mature cells was observed in both the erythropoietic and granulopoietic series in the bone marrow (see table).

The marrow index of maturation of neutrophils and erythroblasts in the experimental animals receiving orotic acid in a dose of 100 mg/kg was only half that in the control animals.

Analysis of these results, taking into account the data published in the literature, suggests that the effect of orotic acid causing differentiation of the cells of the granulopoietic and erythropoietic series of the bone marrow may be due to an increase in enzyme activity, namely to its action on dehydro-orotate dehydrogenase [1, 9]. The possibility is not ruled out that excessive administration of orotic acid affects the amino-acid balance in the body, which in turn modifies the functional activity of the enzyme systems. In these conditions the formation of "retroinhibitor enzymes" is possible, and these may take part in metabolic processes associated with the maturation of the blood cells.

It may therefore be concluded from these results that orotic acid may be used to stimulate maturation of the cells of the erythropoietic and granulopoietic series in the bone marrow.

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