8998 P

Mechanism of Cobalt Polycythemia. Effect of Ascorbic Acid.

ALBERTO GUZMAN BARRON AND E. S. GUZMAN BARRON.

From the Lasker Foundation for Medical Research and the Department of Medicine, University of Chicago.

Waltner and Waltner[1] discovered that cobalt when given to animals produced a polycythemia as shown by the increase in the number of red cells and in hemoglobin. Mascherpa[2] from studies of cobalt polycythemia on dogs reported an increased activity of the bone marrow. For experiments on the mechanism of this polycythemia rabbits were used so that blood could be withdrawn in sufficient quantities to measure the hemoglobin concentration and count the red cells simultaneously. By daily subcutaneous injection of 0.01 gm. $CoSO_4$ a definite polycythemia was produced within 6 or 7 days, accompanied by the appearance in the circulating blood of reticulocytes and erythroblasts. The presence of these young cells was strikingly manifested by the increased respiration of red cells from animals with cobalt polycythemia, an increase which fails to appear in human polycythemia vera (Table I). The increase in respiration was about 10 times as great when erythroblasts were present.

TABLE I.

O_2 Consumption of Red Cells from Polycythemia.

pH, 7.38; T., 37° C. Figures were calculated for blood containing $5x10^6$ red cells per cmm. 2 cc. per vessel.

Kind of Blood	O_2 Consumption cmm. per hour	Reticulocytes %	Erythroblasts %
Rabbit			
Control	4.3	2.06	—
Co polycythemia	11.9	9.27	—
" "	45.0	6.66	4
Man			
Polycythemia vera	5.3	0.2	—

The addition of $CoSO_4$ (0.01 mg.) *in vitro* to the red cell suspensions from cobalt polycythemia was followed by a marked inhibition in respiration as contrasted with the lack of such effect in the red cells of normal rabbits. This inhibition was practically confined to the respiration of immature red cells, being greater in the bone marrow than in the spleen and kidney (Table II).

1 Waltner, K., and Waltner, K., *Klin. Woch.*, 1929, **8**, 313.

2 Mascherpa, P., *Arch. ital. biol.*, 1930, **82**, 112.

TABLE II.

Kind of Tissue (Rabbit)	O_2 Consumption—cmm. per hour		
	Before	After Addition of $CoSO_4$	Inhibition %
Red cells (Co polycythemia)	10.7	3.9	63.6
" " " "	14.4	1.1	92.0
" " " "	50.2	5.1	89.8
" " normal	4.4	4.8	none
Bone marrow	20.8	12.9	38
Spleen	27.5	25.0	9.1
Kidney	41.5	36.7	8.9

The findings of Berwald, Arsenau, and Dooley[3] that cobalt fails to produce polycythemia in splenectomized rats did not hold in the case of rabbits, a discrepancy which may be explained by the fact that splenectomized rats develop an anemia by *B. muris*.

Ascorbic acid seems to assist in the maintenance of a determined level of red cells in the circulating blood, this effect in certain cases of anemia having been reported many times. When ascorbic acid was injected intravenously into the rabbits (60 mg. daily) simultaneously with $CoSO_4$, polycythemia failed to appear; when the ascorbic acid was withdrawn it appeared at the end of 6 or 7 days. When ascorbic acid was injected after the production of polycythemia a decrease in the hemoglobin concentration and red cell count resulted,

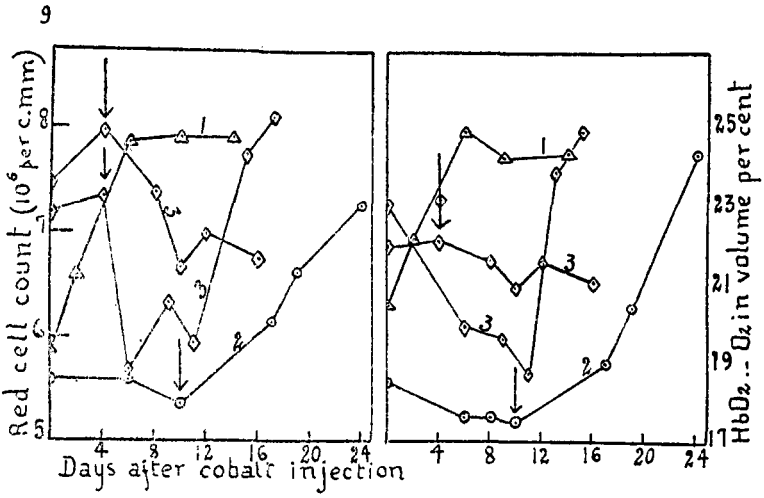

FIG. 1.

1. Control. Injection of $CoSO_4$ alone.
2. $CoSO_4$ and ascorbic acid injected simultaneously. 10 days after (marked by arrow) the ascorbic acid was withdrawn.
3. Cobalt polycythemia treated with daily injections of ascorbic acid.

[3] Berwald, W. P. E., Arsenau, J. H., and Dooley, M. S., PROC. SOC. EXP. BIOL. AND MED., 1934, **32**, 430.

although the effect was temporary (Fig. 1). The concentration of hemoglobin ran in all experiments parallel to the red cell count.

According to these experiments cobalt polycythemia seems to be due to the inhibition by cobalt of the respiratory function of immature red cells. Once these cells have lost their ability to respire they are thrown into the general circulation as mature non-respiring cells, being replaced in the bone marrow by new cells. The function of ascorbic acid as one of the regulators of the level of red cells in the circulating blood seems probable in the light of these experiments.

8999 C

Participation of Ovarian Factors Other than "Estrin" in the Estrus Phenomenon.

S. C. FREED, T. GARVIN AND SAMUEL SOSKIN.

From the Department of Metabolism and Endocrinology, Michael Reese Hospital, Chicago, Illinois.*

We have recently shown that the evaluation of the potency of estrogenic substances cannot be based solely on the ability of these substances to cause vaginal cornification in test animals. Other physiologic effects, perhaps more important from a therapeutic standpoint, must also be considered.[1] However, even if the various activities of the known estrogenic substances were available to a high degree in a single "estrin", it would still be doubtful whether this estrin could serve therapeutically as a perfect substitute for the normal ovary, in bringing about the estrus phenomenon.

Aside from teleological reasoning based on its site of origin, the estrogenic substance elaborated by the ovarian follicle† merits consideration as being the true estrus hormone chiefly because its administration to castrate animals results in a state which resembles spontaneous estrus in the intact animal. With neither this nor any other estrogenic substance, however, has it been possible to reproduce in castrate animals a certain phase of estrus which has been

* Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1 Freed, S. C., and Soskin, Samuel, *Endocrinology*, 1936, **20**, 863.

† Recently identified as dihydroxyestrin.[3]

3 MacCorquodale, D. W., Thayer, S., and Doisy, E., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1182.