The causative mechanism responsible for congestive heart failure may well be due to the above mentioned two hemodynamic factors which were brought forth by propranolol.

Summary. The effect of propranolol on the peripheral vascular beds was studied in anesthetized dogs in which the regional artery was perfused constantly with arterial blood using a Sigmamotor pump. It was found that the effect of the intra-arterial administration of propranolol on the peripheral vascular beds is biphasic, an initial, rapid decrease in perfusion pressure (vasodilatation) being followed by a prolonged increase (vasoconstriction) without any change in the systemic circulation. The initial vasodilator effect was not blocked either by atropine, DCI or by repeated injections of propranolol which sufficiently blocked the effect of isoproterenol on the vessel.

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Use of Mild Plethora to Demonstrate an Erythropoietic Effect from Small Amounts of Androgens. (30577)

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It has been shown that testosterone increases erythropoiesis in polycythemic mice (1). It also increases erythropoietin production, particularly after stimulation with cobalt (2) or hypoxia(3,4). On the basis of this evidence it has been postulated that testosterone may, at least in part, stimulate erythropoiesis by its effect on erythropoietin production. This implies that testosterone's effect on various refractory anemias may also be mediated by an increase in erythropoietin production. A frequent criticism of this conclusion has been that the doses of testosterone being used were extremely large. We have recently reported that increasing degrees of plethora dampen the erythropoietic effect of testosterone(5). In the present paper we shall present evidence that small doses of testosterone can be shown to exert an erythropoietic effect.

Methods. Ten- to 12-week-old CF No. 1 female mice weighing 23-26 g were used.

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† Operated by Univ. of Chicago for U. S. Atomic Energy Commission.

TABLE I. Effect of Small Doses of Testosterone on Mildly Plethoric Mice.

0.2 xx RBC X 2	No. of animals	Hemato-crit	Fe^{59} uptake ± S.E.
Sesame	7	47 ± .5	1.9 ± .3
.1 mg testosterone	6	47 ± 1	4.5 ± .8
.25 " "	8	47 ± 1	8.8 ± 2.1
.50 " "	8	50 ± 1.6	11.7 ± 1.9
1.0 " "	7	48 ± 1.2	21.4 ± 3.2

Testosterone propionate was diluted in sesame oil to provide the desired dose in a volume of 0.1 cc.

Mouse erythrocytes were collected, washed once and resuspended in saline in 80% concentration. The indicated volume of packed RBC's was given on each of 2 consecutive days. Testosterone was administered subcutaneously on the same days. One-half microcurie of radioiron was given intravenously 96 hours after the final injection of testosterone, and the 72-hour radioiron incorporation into newly formed erythrocytes was determined and expressed as a percentage of the injected dose.

Mice were made hypoxic by placing them for 8 hours in an evacuated chamber of the type described by Bangham and Cotes(6). The pressure was set at 60% of atmospheric pressure.

Erythropoietin titers were assayed using the polycythemic mouse assay described by DeGowin *et al*(7).

Results. Effect of testosterone on mildly plethoric mice. This experiment compares the effects of various doses of testosterone on erythropoiesis of mildly plethoric mice. Plethora was induced by injecting 0.2 cc of packed red cells daily for 2 consecutive days. Testosterone in the dosage indicated in Table I was injected on the same days as transfusion. Results indicate that 2 injections of 0.1 mg of testosterone are sufficient to stimulate erythropoiesis in mildly plethoric mice, and the degree of erythropoietic stimulation increases as the dose increases. One milligram of testosterone increases erythropoiesis to more than 11 times the control value.

Effects of small doses of testosterone on erythropoietin titers of hypoxic mice. In this experiment we studied the effects of small doses of testosterone on the erythropoietin titers of hypoxic mice. Mice were injected with either 0.25 mg of testosterone or 0.1 cc of sesame oil on each of 2 consecutive days. Forty hours after the final injection, some of the animals were placed in an environment maintained at 60% atmospheric pressure for 8 hours. Immediately on return to ambient pressure, they were exsanguinated and the plasma assayed for erythropoietin. The plasma of non-hypoxic mice was collected 48 hours after the second injection of testosterone or sesame oil and assayed for erythropoietin. The results are shown in Fig. 1. The erythropoietin titers of hypoxic mice treated with 0.25 mg of testosterone are 3 times higher than those of hypoxic mice treated with sesame oil. Mice treated with 0.25 mg of testosterone but not made hypoxic did not have detectably elevated erythropoietin titers.

Discussion. Testosterone stimulates erythropoiesis in polycythemic mice and does so, at least partially, by increasing erythropoietin production(3,4). A frequent objection raised against applying these studies to the interpretation of the effect of testosterone on human erythropoiesis has been that extremely large doses of testosterone have been employed.

Previously we have shown that the effect of testosterone on erythropoiesis is more marked in mildly plethoric mice(5). Consequently, using only mildly plethoric mice, we have reinvestigated the minimal dose of testosterone necessary to observe a detectable erythropoietic effect. We have shown here that as little as 0.1 mg of testosterone given on 2 consecutive days produces an increase

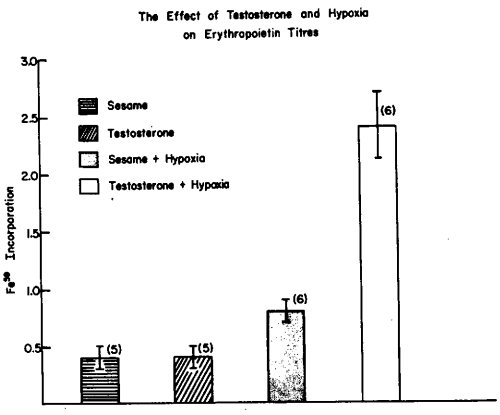

FIG. 1

in the erythropoietic rate. On a per weight basis this dose is comparable to doses administered in human disease. Since the effect of testosterone increases with decreasing plethora, one might expect that even smaller doses would affect the non-plethoric mouse, although their effects would be diffcult to detect because they would be masked by the high basal rate of erythropoiesis.

The results reported above also indicate that as little as 0.25 mg of testosterone produces measurable increases in the erythropoietin titers of hypoxic mice. These studies make it unlikely that effects on erythropoiesis and erythropoietin formation are due only to some non-specific effect of extremely large doses of testosterone.

The above experiments also emphasize the value of mildly plethoric mice for the study of erythropoietic stimuli which are dependent on erythropoietin for their effect. Triiodothyronine(4), cobalt(8) and testosterone all have a more profound effect on the rate of erythropoiesis of mildly plethoric mice than on mice made more intensely plethoric.

While it may be premature to interpret the role of testosterone in the therapy of human anemias on the basis of these experiments in mice, the demonstration that doses of the hormone that are effective in the mouse are comparable to those used in the clinics, encourages us to investigate the effect of testosterone on erythropoietin levels in anemic patients.

Summary. Two daily injections of as little as 0.1 mg testosterone are capable of stimulating erythropoiesis in mildly plethoric mice. Twenty-five hundredths of a milligram of testosterone is sufficient to elevate the erythropoietin titers of hypoxic mice.

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Urea Reabsorption by the Proximal Tubule of the Dog.* (30578)

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Both micropuncture and tissue analytical techniques have been used extensively to study urea reabsorption by the renal tubule of the rat(1-3). These procedures have made it possible to quantitate urea reabsorption in various portions of the rat renal tubule. However, in the dog, the percentage contribution of various portions of the nephron to urea reabsorption has not yet been documented. For this reason, simultaneous renal micropuncture and renal clearance techniques were used in the following experiments to study urea reabsorption by the proximal tubule of the dog.

Methods. Nine micropuncture experiments were performed on normal anti-diuretic dogs anesthetized with pentobarbital (30 mg/kg). The surgical procedure and the technique of renal micropuncture in this species have been described(4). After the urine flow has stabilized, serial urine samples of 15 minutes duration were obtained during the collection of samples of proximal tubular fluid. Blood was drawn at the mid-point of each collection period and concentrations of inulin and urea

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