ment of IRC 741 cells for folic acid. This is comparable to folic acid requirements found in other animal leukemias(12); in this laboratory, L1210 leukemia and the Shay chloroleukemia were found to require approximately 1250 and 830 mμM folic acid, respectively.

IRC 741 cell cultures should be useful for metabolic and chemotherapeutic studies, especially since irradiation, chemicals, and culture conditions provide possibilities for creating variants of the basic cell line. The high degree of stability of the cell line in relation to such phenomena as chromosome numbers, metabolic markers, the high requirement for folic acid, and pathogenicity for rats may prove to be a valuable characteristic of IRC 741 *in vitro*.

Summary. Long-term *in vitro* culture of IRC 741 rat leukemia has been accomplished. During one and a half years in culture, the cell line has remained notably stable in relation to chromosome constitution, high folic acid requirement, growth kinetics, and rat pathogenicity.

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Effect of Propranolol on the Peripheral Circulation.* (30576)

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A newly synthesized compound, propranolol, was found to be a very potent, beta-receptor adrenergic blocking agent(1-3). Since the drug blocks the vasodilator (beta-receptor stimulating) effect of catecholamines without affecting the vasoconstrictor (alpha-receptor stimulating) property, it may be expected that propranolol would not cause vasodilatation of the peripheral vessels. However, Prichard and Gillam(4,5) recently found that propranolol lowered arterial blood pressure significantly in hypertensive patients. The present study was undertaken to investigate the effect of propranolol on the peripheral vascular bed using a technique in which the perfusion blood flow rate was kept constant in anesthetized dogs.

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Methods. Dogs weighing between 20.5 and 26.5 kg were anesthetized with the intravenous injection of sodium pentobarbital (30 mg/kg). In open chest dogs, a femoral artery was perfused with arterial blood at a constant and known rate by means of a Sigma-motor pump as described previously(6). Mean systemic arterial and femoral arterial perfusion pressures were measured continuously with Statham pressure transducers (P23AA). In this set-up, the effect of the drug on the peripheral vascular resistance was evaluated readily by the changes in the perfusion pressure. Heart rate and myocardial contractile force were measured continuously with an Electronics for Medicine (EFM) tachometer and with a Walton-Brodie strain gauge arch(7,8) which was sutured to the right ventricular muscle. All parameters ex-

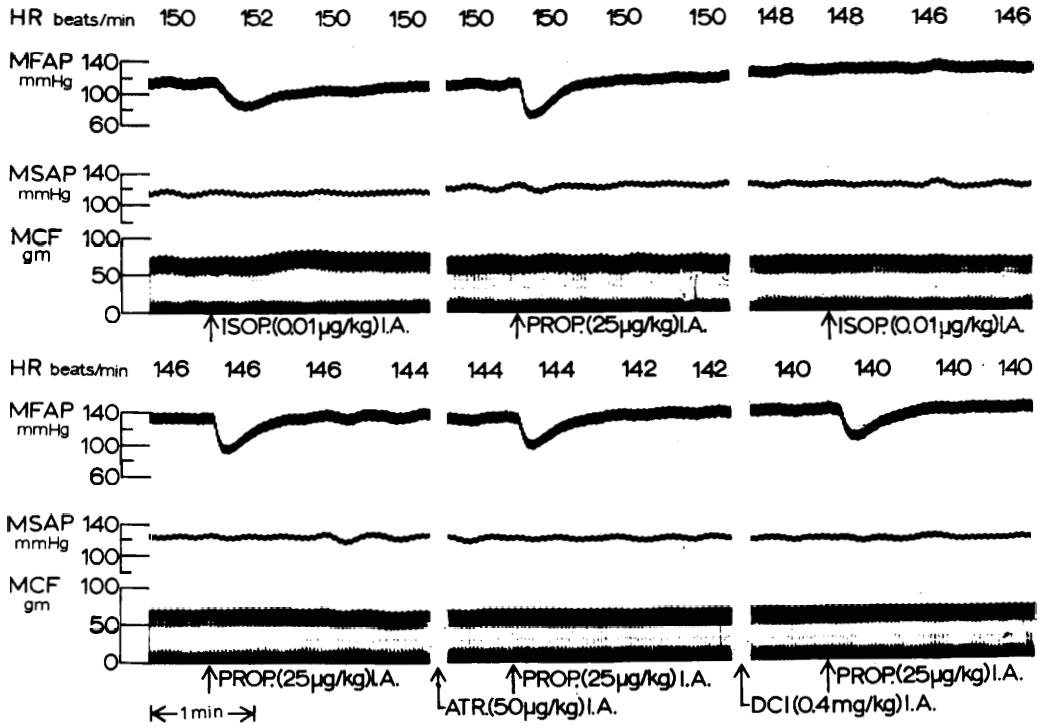

FIG. 1. Effects of intra-arterial (i.a.) administration of isoproterenol (ISOP) and propranolol (PROP) on heart rate (HR), mean femoral arterial perfusion pressure (MFAP), mean systemic arterial pressure (MSAP) and myocardial contractile force (MCF) in a dog. ATR and DCI denote atropine and dichloroisoproterenol, respectively. Throughout a period of the experiment, femoral arterial blood flow was kept constant at a rate of 110 ml/min using a Sigmamotor pump.

cept heart rate were recorded continuously with an EFM recorder (DR 8).

Results. The effect of propranolol on the circulation in the hind-limb was studied in 16 dogs. The results are consistent in all experiments. Tracings of a representative experiment are illustrated in Fig. 1. The effect of the intra-arterial injection of propranolol (25 μg/kg) on the femoral arterial perfusion pressure was biphasic. The drug initially decreased the perfusion pressure markedly and rapidly, but, within one minute, the pressure began to increase and usually stabilized at a level slightly higher than control within 2 to 3 minutes. Since the femoral arterial blood flow was kept constant by means of a Sigmamotor pump and the systemic arterial pressure remained essentially unchanged throughout a period of the experiment, these biphasic changes in the perfusion pressure indicate that propranolol caused a transient vasodilatation initially and subsequently a sustained vasoconstriction. Propranolol blocked completely the vasodilating effect of intra-arterial administration of isoproterenol (0.01 μg/kg). However, the repeated administration of the same dose (25 μg/kg) of propranolol caused essentially the same degree of vasodilatation as the initial injection (Fig. 1). This effect was not modified by the intra-arterial injection of atropine (0.05 mg/kg) or dichloroisoproterenol (DCI) (0.4 mg/kg). The magnitude of the transient vasodilatation induced by propranolol was essentially proportional to the dose given (Fig. 2), but the subsequent vasoconstriction became less striking with repeated aministrations of the same dose (25 μg/kg) of propranolol. However, as shown in Fig. 3, intravenous administration of much larger doses (more than 250 μg/kg) of propranolol caused a much greater rise in perfusion pressure after the initial fall. In addition, the larger doses of propranolol always decreased heart rate and myocardial

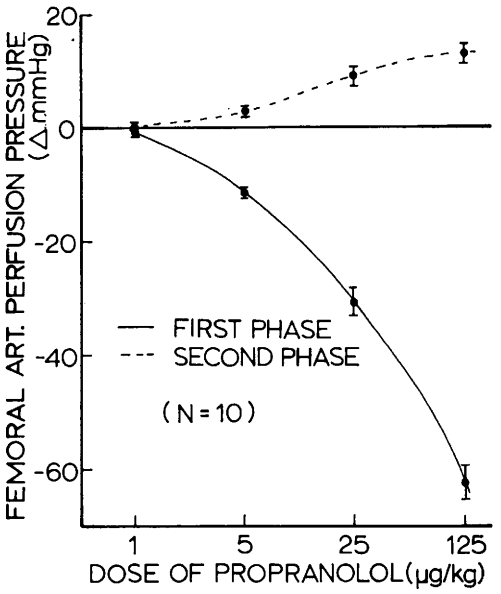

FIG. 2. Effects of the i.a. administration of geometrically increasing doses (0.04-125 μg/kg) of propranolol on femoral arterial perfusion pressure in 10 dogs, in which femoral arterial blood flow was kept constant. Each dot represents mean value of changes in perfusion pressure in 10 dogs. Standard errors of mean are indicated by vertical I-shaped bars.

contractile force and increased left atrial pressure markedly. During this period, mean systemic arterial pressure always decreased slightly and then recovered toward control.

Discussion. From the present study, it is obvious that intra-arterial administration of a small dose or propranolol dilates the regional arteries transiently before constricting the vessels(2,9). The initial vasodilatation observed is apparently due neither to stimulation of the adrenergic beta-receptor nor to that of cholinergic vasodilator fibers(10), since this effect is not modified by the intra-arterial injection of DCI or atropine or repeated doses of propranolol. The magnitude of the vasodilatation induced by propranolol is essentially proportional to the dose given. On the other hand, administration of larger doses of propranolol increases the regional and total peripheral resistances by constricting the regional resistance vessels probably through the indirect stimulation of the adrenergic alpha-receptor. This stimulation is caused by the increased reflex sympathoadrenal activities since the larger doses of propranolol always decrease myocardial contractility, stroke volume and cardiac output markedly(2,3), thereby decreasing mean systemic and pulse pressures(11,12). Very recently, Prichard and Gillam(4) and Prichard(5) reported that propranolol may be useful for the management of essential hypertension. Although, from the present study, propranolol initially decreases the peripheral vascular resistance, the duration of the action is extremely short to be effective in the treatment of essential hypertension. After this transient vasodilatation, propranolol causes a persistent vasoconstriction. Since propranolol causes (a) an increase in total peripheral resistance and (b) a decrease in cardiac performance (2), it is rather difficult to understand the precise mechanism responsible for the clinical alleviation of essential hypertension. Recently, it was reported that propranolol may cause congestive heart failure in some patients(13).

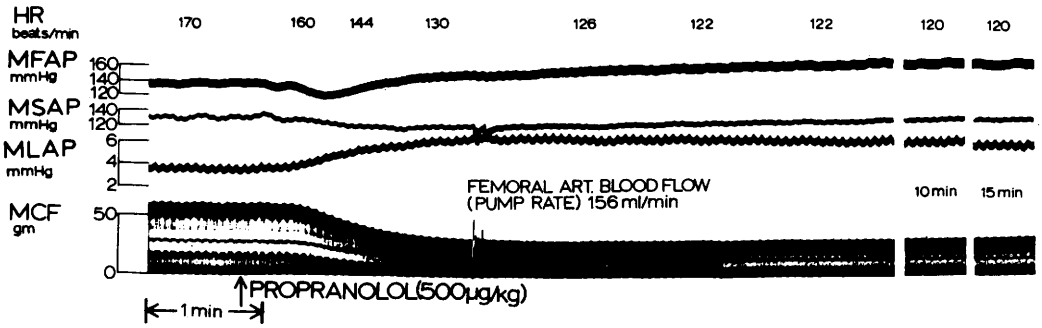

FIG. 3. Effect of intravenous administration of propranolol (500 μg/kg) on heart rate, mean femoral arterial perfusion pressure, mean systemic arterial pressure and mean left atrial pressure (MLAP) and myocardial contractile force in a dog in which femoral arterial blood flow was kept constant at a rate of 156 ml/min throughout a period of the experiment.

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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