quency with which it may be used make it a plan well suited to such a purpose and the investigation is anticipated. The possibility exists, therefore, that uterine clearance times may be done clinically.

Summary. One important reason for measuring uterine circulation throughout pregnancy lies in the possible relationship between ischemia of the gravid uterus and the late toxemias such as pre-eclampsia and eclampsia. We have shown a method of calculating uterine circulation by its ability to clear a radiopaque dye injected by means of a Hypospray into the myometrium. It is shown that the technic can be repeated frequently, is painless and attended by no harmful or uncomfortable sequellae. It is being adapted to human studies.

The authors are indebted to the R. P. Scherer Corp., Detroit, who manufactured the Hypospray used in these experiments, and kindly made it available to us.

17046

Inhibition by Piperidinomethyl-3-benzodioxane (933F) of Epinephrine Vasopressor Blockade Produced by Dibenzyl-β-Chlorethylamine.

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A consideration of the chemical and spatial configuration of compounds which block the pressor action of epinephrine suggests that in all probability dibenzyl-β-chlorethylamine (Dibenamine), ergotoxine, yohimbine, and the phenoxyethylamine type compounds, all block the pressor action of epinephrine by acting on the same mechanism. 933F and ergotoxine have been shown to compete with epinephrine over a wide range of concentrations in isolated physiological systems.[1,2] According to theoretical considerations, ergotoxine, yohimbine, and the phenoxyethylamine type compounds all compete with epinephrine for a receptor of the amine-alcohol configuration in epinephrine. The blocking of this receptor is believed to block the pressor action of epinephrine. Dibenamine is thought to combine chemically with, or near, this same amine-alcohol receptor.

It has been shown by Nickerson and Goodman[3] that the blocking action of Dibenamine is irreversible, in that large doses of epinephrine cannot break through its blocking action and cause a pressor response. This irreversible blocking action persists for 3-5 days after the administration of Dibenamine, by which time more epinephrine receptor is presumed to have been formed. These same authors point out that during the first hour or so after its administration Dibenamine decomposes to a physiologically inactive compound and that all the effects of Dibenamine are due to that fraction which combined with the epinephrine receptors before decomposition occurred. If during this first hour the epinephrine receptors are occupied by a compound which blocks reversibly the action of epinephrine, the Dibenamine should be unable to combine with the receptors and on removal of the reversibly-blocking compound epinephrine should give a normal pressor response. 933F is just such a reversibly-blocking compound which in doses of 5 mg/kg blocks the vasopressor action of epinephrine for 4-5 hours.

Methods. Dogs of either sex under light sodium pentobarbital anesthesia were used for all experiments. The carotid blood pressure was recorded by a mercury manometer. Injections were made into an exposed femoral vein. The 933F was dissolved in a few cc of saline. The Dibenamine was made up 5-20 minutes before use in about 20 cc of saline made strongly acid with hydrochloric

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1 Abdon, N. O., Hammarskjold, S. O., *Acta Physiol. Scand.*, 1940-41, **1**, 85.

2 Gaddum, J. H., *J. Physiol.*, 1926, **61**, 142.

3 Nickerson, M., Goodman, L. S., *Fed. Proc.*, 1948, **7**, 397.

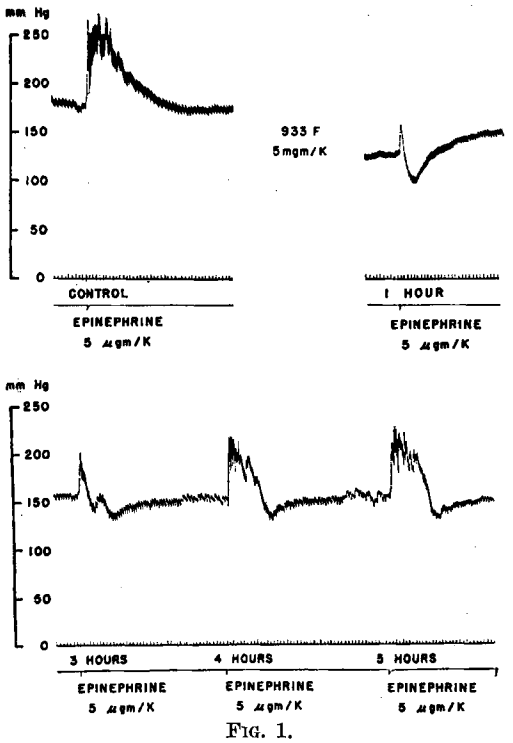

FIG. 1.

Dog, 10.2 kg, female. Sodium pentobarbital anesthesia 30 mg/kg. From top to bottom: carotid blood pressure, 6-second time intervals, injection marker. The 5 blood pressure responses to 5 μg/kg of epinephrine are (reading from left to right): one of 3 control responses obtained before the injection of 933F, and respectively, the responses obtained 1, 3, 4, and 5 hours after the injection of 5 mg/kg of 933F.

acid. The epinephrine used was that available commercially in 1 cc ampules and was diluted 1:10 with saline before injection. All animals were first tested for their response to 3 successive doses of 5 μg per kg of epinephrine. The 933F or Dibenamine was then given and the response of the carotid pressure to 5 μg/kg of epinephrine recorded at hourly intervals thereafter. When both 933F and Dibenamine were injected, the administration of the former drug preceded that of the latter by 3 minutes.

Results. Fig. 1 is a record of the tracings obtained with 5 mg/kg of 933F. By the end of 5 hours the magnitude and duration of the pressor response to 5 μg/kg of epinephrine has returned almost completely to that of the responses obtained before the injection of 933F. Fig. 2 is a record of the tracings obtained with 10 mg/kg of Dibenamine. By the end of 5 hours epinephrine still causes a marked depressor response and there are no signs of return of the initial pressor response. Fig. 3 is a record of the tracings obtained when 5 mg/kg of 933F was given followed in 3 minutes by 10 mg/kg of Dibenamine. The recovery of the pressor response to epinephrine follows essentially the same course as that found after the injection of 933F alone. There is no evidence that Dibenamine exerted any action whatsoever.

In other experiments 5 mg/kg of 933F was given and followed by an infusion of 0.2 mg/kg/min. of 933F for one hour. Recovery of the pressor response to 5 μg/kg of epinephrine was far from complete at the end of 7 hours; however, good pressor responses were obtained from 50 μg/kg of epinephrine. The administration of 20 mg/kg of Dibenamine 3 minutes after the initial dose of 933F de-

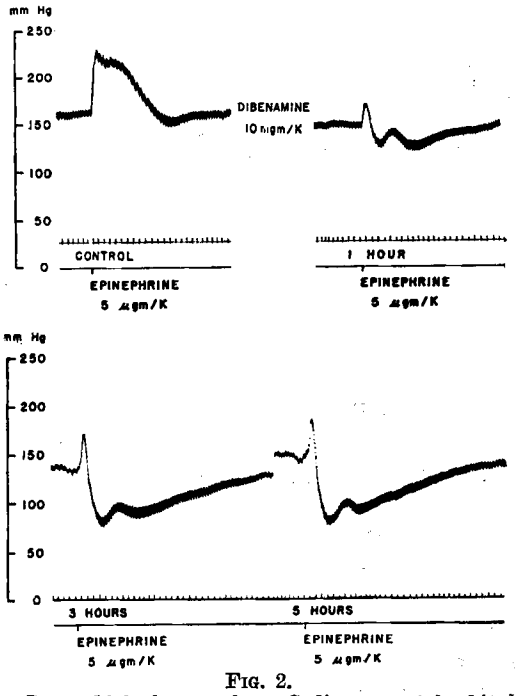

FIG. 2.

Dog, 11.8 kg, male. Sodium pentobarbital anesthesia 30 mg/kg. From top to bottom: carotid blood pressure, 6-second time intervals, injection marker. The 4 blood pressure responses to 5 μg/kg of epinephrine are (reading from left to right): one of 3 control responses obtained before the injection of Dibenamine, and respectively, the responses obtained 1, 3, and 5 hours after the injection of 10 mg/kg of Dibenamine.

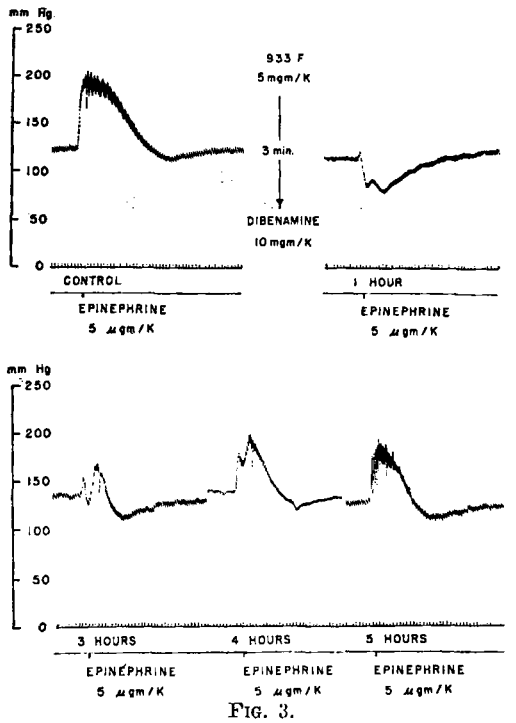

FIG. 3.

Dog, 13.8 kg, female. Sodium pentobarbital anesthesia 30 mg/kg. From top to bottom: carotid blood pressure, 6-second time intervals, injection marker. The 5 blood pressure responses to 5 μg/kg of epinephrine are (reading from left to right): one of 3 control responses obtained before the injection of 933F and Dibenamine, and, respectively, the responses obtained 1, 3, 4, and 5 hours after the injection of 5 mg/kg of 933F followed in 3 minutes by 10 mg/kg of Dibenamine.

pressed only slightly the rate of recovery of the pressor response to epinephrine from that obtained with 933F alone.

Discussion. The fact that 933F prevents Dibenamine from blocking the vasopressor effect of epinephrine may be interpreted in either of two ways. 1. The 933F may aid in the destruction of Dibenamine by either chemically combining with the Dibenamine or enabling something else to do so. 2. The 933F may prevent the Dibenamine from combining with the epinephrine receptors by protecting the receptors. From theoretical considerations and experiments now in progress the latter is considered to be the more likely explanation.

Summary. 5 mg/kg of 933F will prevent 10 mg/kg of Dibenamine from blocking the vasopressor effect of epinephrine in the dog.

The 993F used in these experiments was supplied by Dr. John E. Howard, who obtained it through the courtesy of E. Fourneau.

17047

Contamination of Commercial p-Aminohippuric Acid with p-Aminobenzoic Acid.

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While investigating the oral administration of p-aminohippuric acid (PAH) in man for the purpose of renal clearance measurement, it was noted that different samples of PAH, when administered according to the same routine, gave markedly different concentrations of chromogen in the plasma. PAH was determined by the method of Smith *et al.*[1] in a cadmium sulfate filtrate of plasma.

The plasma concentration of chromogen following the ingestion of 5-6 g of material in divided doses averaged 2.4 mg % (expressed as PAH) in 23 subjects receiving lot No. 12322* while the plasma concentration of chromogen averaged 0.22 mg % in 14 subjects receiving lot No. 236518.* Four tests were then performed on 2 subjects so that

1 Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M., *J. Clin. Invest.*, 1945, **24**, 388.

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