quantitatively and are a poor criterion for estrogen activity.

Discussion. These studies confirm previous observations that injections of estrogen stimulated increased alkaline phosphatase activity in certain tissues associated with reproduction in rodents.[1,3-6] They also call attention to one of the heaviest deposits of active phosphatase in the rat—that seen in the stratified epithelium lining the lumen of the cervix. In addition, the appearance of enzyme activity after injection of estradiol is noted in the endometrial stroma of the uterus and upper cervix, in contrast to that reported for the mouse.[2] Such activity has, however, been reported for the endometrial stroma of the pregnant sow.[1]

The significance of the relationship of estradiol to alkaline phosphatase in normal reproductive physiology is not known. The enzyme is known to be concerned with calcium metabolism as well as that of phosphorus due to the interrelationship of the two metals in their action in the body. Estradiol is also associated with calcium, causing its removal from some bones while laying it down in others.[7] It is highly possible that it may also have a bearing on the calcium metabolism of certain reproductive tissues. If this be so, it is then conceivable that some of the actions of estradiol may be due to the adjustments of tissue calcium through the relation of the hormone with the enzyme.

Summary. Estradiol causes a spectacular increase in the alkaline phosphatase activity of the genital tract of the rat. This increase is most marked in the stratified epithelium lining the lumen of the cervix, but it is also apparent in the connective tissue cells of the stroma of uterus and uterine cervix and in the circular musculature of the upper part of the genital tract.

In contrast to the stratified epithelium of the cervix and of the vagina, the columnar epithelium of the uterus shows very little phosphatase activity in the presence or absence of estradiol stimulation.

6 Talmage, R. V., *Anat. Rec.*, 1947, **99**, 15.

7 Gardner, W. U., and Pfeiffer, C. A., *Physiol. Rev.*, 1943, **23**, 139.

17045

Uterine Circulation Time in the Pregnant Primate, With the Uterus and Abdomen Intact.

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The determination of uterine circulation rate in the pregnant primate is of considerable importance. Recent investigation has led many authorities to believe that there is a relationship between abnormal uterine circulation and the late toxemic syndrome. The abnormality of circulation is considered to be uterine ischemia but this has never been demonstrated. Page[1] in discussing this theory of toxemia has stated that it is unfortunate that no one has been able to determine uterine circulation times throughout pregnancy. Moreover, Smith and Smith[2] consider that the hormonal changes they find in pre-eclampsia are the result of placental ischemia which is attributable, in turn, to uterine ischemia. The basic cause of this ischemia, which apparently develops late in pregnancy, is another matter. Page[1] lists a group of conditions such as hydromnios, multiple pregnancy, diabetes, etc., in which he feels uterine ischemia is most likely to occur and, indeed, toxemia is frequently found in such conditions

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1 Page, E. W., *Obs. and Gyn. Survey*, 1948, **3**, 517.

2 Smith, O. W., and Smith, G., *Am. J. Obs. and Gyn.*, 1949, **56**, 821.

as he mentions. Most often, however, no direct relationship with other pathological processes is observed. Recently a mechanism of physiological growth patterns and shapes in the uterus of pregnant rabbits has been described, aberrations from which would produce myometrial ischemia in the latter part of pregnancy.[3] Comparable changes in the growth and shape of the uterus have been observed to occur in the monkey[4] and in the human.[5] In order to test these findings in the primate and to support or negate the ischemic theory described above, we have evolved a method of studying uterine circulation with the abdomen and uterus intact, at regular intervals throughout pregnancy.

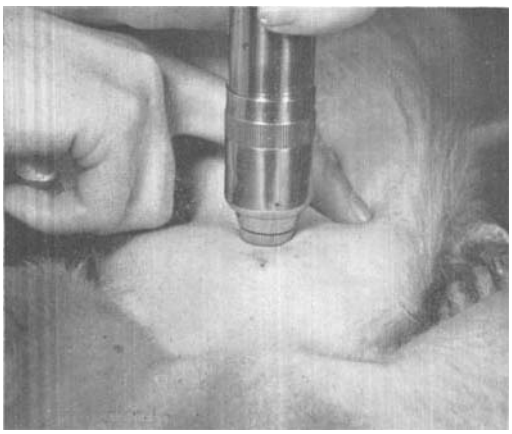

FIG. 1.
The Hypospray shown above will hold up to 1 cc of liquid. Thionine blue is being injected through the abdominal wall of a monkey 60 days pregnant.

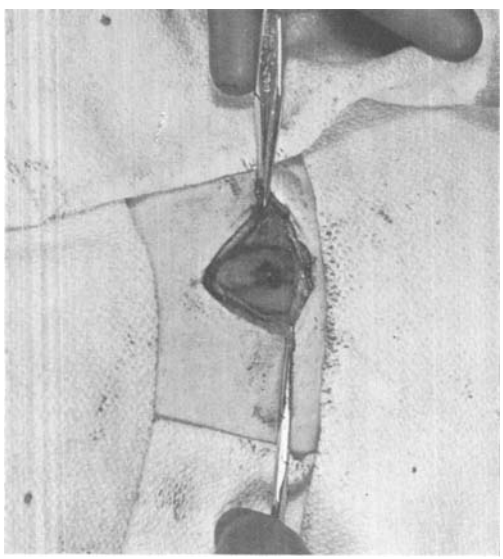

FIG. 2.
At laparotomy uterus of monkey shown in Fig. 1 is seen to contain drug injected through anterior abdominal wall. This is merely a demonstration technic.

Method. The technic described is based upon the ability of uterine muscle to clear a certain amount of dye compared to the ability of the muscle of the anterior abdominal wall to clear an equal amount of the same substance. By use of a new jet injection hypodermic called a "Hypospray" it is possible to propel drugs under the skin almost without pain. The depth of penetration depends upon the strength of the thrust developed which can be controlled by the operator. The Hypospray used in these experiments is modified from the original model described by Hingson[6] in that it is more powerful and can inject a greater amount of drug (1 cc).

The pregnant monkey uterus can be felt abdominally by the fortieth day (duration of gestation—160 days). From this time forward it is possible with a Hypospray to propel a fixed amount of Diodrast into the uterus and an equal amount into the anterior abdominal wall at another injection site. By means of serial x-rays the rate of disappearance of each injection may be observed and charted. The procedure may be performed as often as twice weekly on the same animal without evidence of damage to mother or fetus. Placental separation has not occurred even though there is nearly always an anterior implantation of a secondary placenta in monkeys. The animals gave no sign of a response to pain at the time of injection and such injections have been shown to be practically painless to humans.

A series of preliminary observations has

[3] Reynolds, S. R. M., *Am. J. Obs. and Gyn.*, 1947, **53**, 901.

[4] Gillespie, E. C., Ramsey, E. M., Reynolds, S. R. M., *Am. J. Obs. and Gyn.*, in press.

[5] Gillespie, E. C., manuscript unpublished.

[6] Hingson, R., *Analgesia and Anaesthesia*, 1947, **26**, 221.

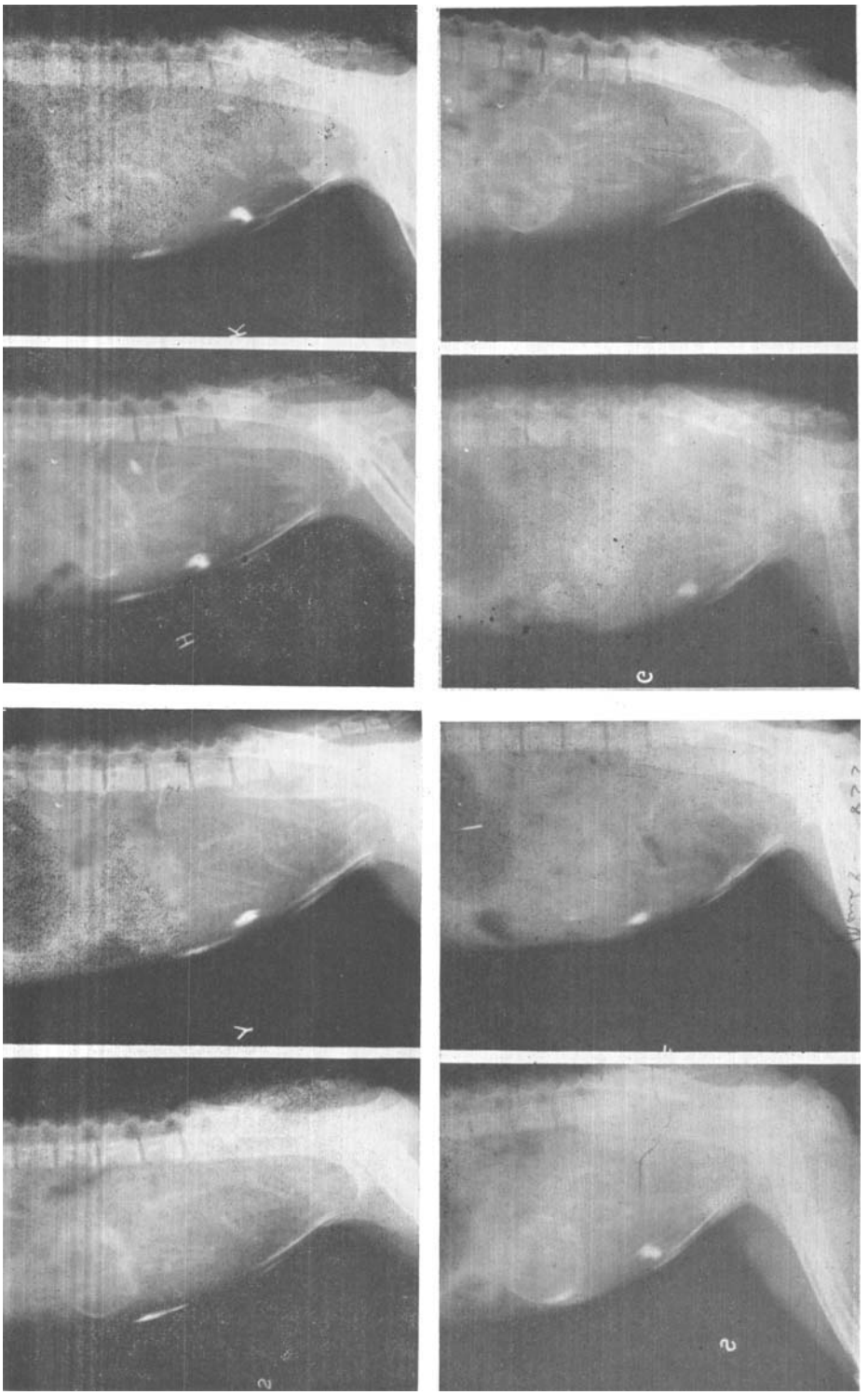

FIG. 3. The x-ray marked (2) was taken immediately following injection of 1 cc of Diodrast into the anterior abdominal wall. The dye can be seen clearly lodged in the rectus muscle just below the level of the fetal head. The x-ray marked (Y) was taken 10 minutes later immediately following the injection of 1 cc of Diodrast into the myometrium. Succeeding x-rays (H, K, S, F, I) were taken at regular intervals until both areas were cleared (1). In the series shown above clearance time for muscle was 25 minutes, and for uterus, 34 minutes. Duration of gestation was 106 days.

been made on monkeys and will be reported later. The technic has been developed in order that it may be adapted to human studies. The absence of pain, and the fre-

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.