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Received February 19, 1953. P.S.E.B.M., 1953, v82.

## Influence of Pregnancy upon Hypertension Induced in Rats by Sodium Chloride and Desoxycorticosterone.* (20148)

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Pregnancy in rats invariably causes a fall of blood pressure when hypertension has been previously induced by a partial constriction of the renal artery(1-3). This reduction of hypertension is manifest in the second half of pregnancy and is maximal just prior to delivery, following which the hypertension returns to the prepregnancy level. The same phenomenon has been observed in dogs(4-6) and in rabbits(2,7). We are not aware of any reports regarding the influence which pregnancy might have upon other forms of experimental hypertension in the rat. Masson, Lewis, Corcoran, and Page(8), however, have stated that the administration of desoxycorticosterone acetate (DCA) to pregnant rabbits results in paralysis or convulsions and hepatic necrosis with subcapsular hemorrhages. Inasmuch as several authors have implicated adrenal cortical-like hormones and sodium chloride in the etiology of human eclampsia (reviewed by Mastboom(9)), the interaction of pregnancy and sodium chloride-DCA hypertension in the rat was studied. Although experimental results in rats are not directly applicable to women, especially because of the recognized differences in placental anatomy and function and the absence of spontaneous toxemia in lower mammals, it was hoped that this study might determine whether there are differences between renal hypertension and sodium hypertension, or whether a syndrome resembling eclampsia might develop in "sodium sensitized" animals.

*Methods.* Adult female rats of the Long-Evans strain were unilaterally nephrectomized, and 60 or 70 mg of DCA in the form of discs or cylinders were implanted subcutaneously, in the manner described by Masson, Corcoran, and Page(10).† The animals were placed on a diet consisting of 3 parts of Purina fox chow and one part of casein supplemented with the known essential vitamins. One per cent sodium chloride solution was supplied as drinking water with special traps to catch any spill. Systolic blood pressures were determined 2 or 3 times a week, using the microphonic method described by Friedman and Freed(11). Fluid intake and urinary output, quantitative proteinuria and body weights were determined frequently. Since the estrus cycles became quite irregular under this regime, males were placed with the females overnight at arbitrary intervals rather than selecting the time on the basis of estrus. Examinations for sperm

* This investigation was supported by research grants from the National Heart Institute of the National Institutes of Health, Public Health Services; and the Edwards Fund. We wish to acknowledge the valuable assistance of Jane O'Connell and Leonard Olson.

† We are indebted to Dr. Ernst Oppenheimer of Ciba, Inc. for a liberal supply of DCA cylinders, 15 mg each, and for DCA powder, from which Dr. G. M. C. Masson kindly prepared discs of 35 mg each.

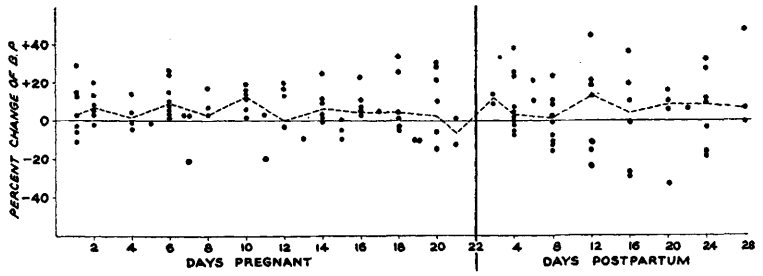


FIG. 1. Percentage change in systolic blood pressure during pregnancy and the puerperium. The zero line represents the mean pressure during the month prior to conception. The dotted line connects the median values.

plugs were made in the morning. After many weeks of failure to find sperm plugs, it was found necessary to substitute tap water for the saline solution during the night of mating. If this were not done, the males became so preoccupied with drinking the salt water that they had either a lack of time or interest in the females.

*Results.* In view of the fact that Burdick and Konanz(12) reported that DCA administered from the time of copulation prevented implantation of fertilized ova in mice, it is of interest to note the pregnancy success rate in the rats. Of 34 females repeatedly placed with males, 14 delivered live litters successfully. Of the remaining 20, only 2 showed definite sperm plugs without evidence of pregnancy. One additional rat became pregnant but died on the 11th day of a ruptured aneurysm of the duodenal artery. Only a few of the mothers attempted to care for their litters, and of these only a portion of 2 litters survived for more than 10 days. This suggests a deficiency of lactation, but the mothers were not sacrificed for histologic examination of the breasts.

Blood pressure readings during successful pregnancies in 12 animals are shown in the scattergram (Fig. 1) as a percentage change over the prepregnancy level. Of these, 7 rats were hypertensive at the time of conception (systolic pressures between 150 and 170 mm Hg) and 5 had pressures only slightly elevated (112 to 126 mm Hg, as compared with the blood pressures of normal control pregnant rats which average 105 $\pm$ S.D. 6 mm Hg). The dotted line connecting the median values for each 2-day interval during pregnancy and the puerperium indicates that pregnancy exerted no influence whatever upon the level of blood pressure. The fact that the median line is slightly (from 2 to 14%) above the prepregnancy blood pressure level can be attributed to the progressive nature of the induced hypertension.

Fig. 2 portrays graphically the changes in urine volume and urinary protein excretion, using the averages for the entire group of animals. The differences in urine volumes from one period to another are not statistically significant. The increases of urinary protein excretion during the second and third trimesters of pregnancy are statistically significant when compared to the antepartum excretion, and the rates of excretion after delivery are significantly higher than the prepregnancy rates.

Since we did not know whether urine volumes or protein excretion changed during normal pregnancy in rats, 12 untreated animals on stock diets and tap water were observed before, during and after pregnancies. The urinary output varied from 11 to 31

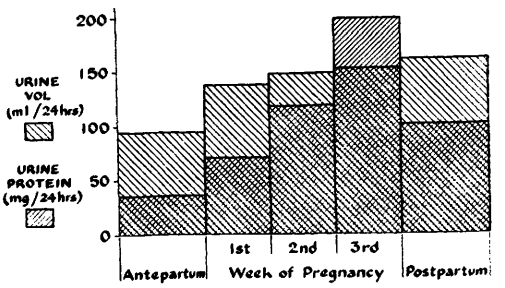


FIG. 2. Mean changes in urine volume and proteinuria during pregnancy and the puerperium in the experimental group.

ml/24 hours, the urinary protein excretion from 4 to 7 mg/24 hours. None of the changes in the group averages was significant.

Observations of body weight and clinical behavior during pregnancy failed to show any evidences of increased edema, muscular irritability or other disturbance in the experimental group as compared to the control group.

*Discussion.* The administration of DCA and sodium chloride to rats causes hypertension, proteinuria, and a very high fluid intake and output. Superimposing the state of pregnancy causes a significant increase of proteinuria in the latter part of gestation, but no change in the blood pressure or fluid balance. The DCA, in dosages large enough to cause hypertension, does not prevent conception, implantation or normal delivery in the rat.

There are many claims that DCA-like hormones play a role in the causation of human eclampsia, and the present experiments shed no light on this question because of species differences. Suffice it to say that a syndrome resembling toxemia cannot be induced by pregnancy in the rat under the conditions employed. If the degree of proteinuria parallels the extent of renal damage in DCA-treated rats, then pregnancy may accelerate this change. The residual increase of proteinuria during the month postpartum, however, may reflect the natural progression of DCA-sodium disease, since a steady increase of renal damage and protein excretion is characteristic of this syndrome.

One of the chief points of interest centers about the differences between the effect of pregnancy upon this disease and that of induced renal hypertension. We concluded previously that the remission of renal hypertension brought about by late pregnancy could not be duplicated by exogenously administered hormones separately or variously combined (13). We also demonstrated that the lowering of blood pressure was due entirely to the placenta and not the fetus(14). The conclusion was reached that the placenta must exert this effect in one of 2 ways; through a "vascular shunt" effect, or through the liberation of an enzyme (such as angiotonase) which neutralized a renal pressor substance.

The vascular shunt effect is common to both groups of experiments; so one might deduce that the only difference resides in the nature of the chemical mediators of the hypertension. The complete absence of a fall of blood pressure late in pregnancy in the DCA-sodium syndrome, therefore, indirectly suggests that the cause of this hypertension is not the same as the cause of experimental renal hypertension.

*Conclusions.* 1. Desoxycorticosterone acetate (DCA) and sodium chloride, in amounts sufficient to cause hypertension do not interfere with conception, implantation or normal delivery in rats. 2. When pregnancy is superimposed upon DCA-sodium hypertension, the blood pressure and fluid balance are not affected. There may be a transient increase of proteinuria during the last third of pregnancy. 3. The failure of the elevated blood pressure to fall during late pregnancy, as it regularly does in experimental renal hypertension, suggests a difference in the chemical mediation of the 2 types of hypertension.

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