

Effects on Parturition in the Rat of Ablation of Different Lobes of the Hypophysis.* (20744)

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Pencharz and Long(1,2) observed that pregnancy in the rat was not interrupted by removal of the hypophysis on or after the 11th day of pregnancy. Parturition was, however, deranged; the rats died or gave birth to dead or living young after a prolonged pregnancy. Selye, Collip, and Thompson(3) reported that gestation was prolonged to 26 days in 22 out of 24 rats hypophysectomized between 10 and 14 days of pregnancy, but that the young were born alive. Pencharz and Long(2) and Smith(4) found that the posterior lobe was not essential for gestation and normal parturition in the rat. Sufficient advances in the preparation and care of hypophysectomized animals have been made since these early studies to justify reopening the subject of the effect of hypophysectomy on the termination of pregnancy. Experience has reduced the time required for the operation and the attendant trauma to tissue. Post-operative care has been improved and includes such measures as special diet, air-conditioning and supplementary injections of glucose and antibiotics. Skill acquired in removing the anterior and posterior lobes separately with precision[†] has also made possible the reanalysis of the effects on parturition of removal of each lobe and antibiotics have been used successfully to decrease post-operative mortality.

Methods. The animals employed were female rats of the Long-Evans strain, 3 to 6 months old, weighing approximately 200 g. The parapharyngeal approach to the hypophysis was used in all operations. This report includes results from a total of 86 rats in which operative procedures were considered successful. The effects of post-operative terramycin injections were tested in 57 of these

rats, which had been subjected to complete hypophysectomy on day 12 or 13 of gestation; 30 of these animals received 4 ml of 125 mg % terramycin in 5% glucose solution on the day of the operation and the subsequent day; the other 27 received no supplement after the operation. The effect on pregnancy and parturition of ablation of the posterior and intermediate lobes was studied in two ways: in 7 rats these lobes were removed 3 to 7 weeks after conception; in 10 other rats the lobes were removed on the 12th day of pregnancy. (The removal of the posterior and intermediate lobes will henceforth be designated as posterior hypophysectomy or ablation of the posterior lobe.) In order to check the effect on parturition of the absence of the anterior lobe only, this lobe was removed in 12 animals on the 12th day of pregnancy. All animals received terramycin post-operatively with the exception of those in the group of completely hypophysectomized rats which were used as untreated controls in the experiments designed to test the action of this antibiotic.

The rats were placed with males in the evening when in heat, estrous being determined by the vaginal smear method. The morning on which sperm were found in the vagina was considered as the first day of pregnancy. The rats were kept in an air-conditioned room (74-78°F). The regular diet (diet XIV), given dry, was supplemented after operation by a wet mash of diet I given daily.[‡] Lettuce was given 2 to 3 times weekly. On the 22nd day of pregnancy the rats were placed in individual cages and observed every few hours for the following 4 days. At autopsy

* Aided by U. S. Public Health Service Research Grant.

† The authors would like to express their appreciation to Attaline McKnight for her skillful assistance in removal of the separate lobes of the pituitary.

‡ Diet XIV consists of 68.5% wheat, 5% casein, 10% fish meal, 10% alfalfa leaf meal, 5% fish oil, 1.5% NaCl, KI added (analysis 1 µg iodine per g diet). Diet I consists of 67.5% wheat, 15% casein, 7.5% skim milk powder, 6.75% hydrogenated vegetable oil, 1.0% fish oil, 0.75% NaCl, 1.5% CaCO₃, KI added (analysis 1 µg iodine per g diet).

TABLE I. Effects on Parturition of Post-Operative Terramycin Treatment in Completely Hypophysectomized Rats.

Treatment	Total	No. of animals— Parturition—		Parturition, %—	
		Normal	Abnormal	Normal	Abnormal
Terramycin	30	12	18	40	60
No terramycin	27	5	22	18	82

TABLE II. Comparison of Effects on Parturition of Removal on the 12th Day of Gestation of the Complete Hypophysis or Its Separate Lobes. (Terramycin given post-operatively.)

Type of operation	Total	No. of rats— Parturition—		Parturition, %—	
		Normal	Abnormal	Normal	Abnormal
Post. lobe removal	10	9	1	90	10
Ant. " "	12	3	9	25	75
Total hypophysectomy	16	4	12	25	75

on day 26 the pituitary site was carefully inspected under a dissecting microscope. The few animals in which there was doubt as to the type or completeness of the operation were discarded. In order to confirm the presence or absence of anterior lobe tissue the mammary glands, ovaries, adrenals, and thyroids were removed and fixed in Bouin's fluid, imbedded in nitrocellulose, sectioned at 7 μ , and stained with hematoxylin and eosin. The condition of the lungs was also checked as possibly pertinent to the question of the resistance of the hypophysectomized rat to the strain of prolonged gestation and parturition. The animals were classified in one of two categories depending on the duration and mode of termination of pregnancy: 1) normal, which included the animals which gave birth at term to living young, without prolonged labor; and 2) abnormal, which included the animals which died shortly before, at, or after term; those which resorbed; and those in which gestation was prolonged by 1 to 3 days.

Results. Effects of terramycin treatment on parturition in completely hypophysectomized rats. Terramycin, injected daily for 2 days post-operatively, definitely increased the number of animals surviving hypophysectomy; 25% of the animals died in the immediate post-operative period if no terramycin was administered, whereas only 5% died when the antibiotic was given.[§] More unexpectedly, there were also increased numbers of survivors after normal parturition in the group receiving terramycin (Table I).

Effects of ablation of whole pituitary and of separate lobes on parturition. When the posterior and intermediate lobes were removed 3 to 7 weeks before the animals were bred, 6 of 7 rats delivered on time (22 to 23 days) without complications. They lactated well. (The seventh animal in the group also appeared to have littered as judged from autopsy evidence.) When the posterior and intermediate lobes were removed on the 12th day of pregnancy, leaving the anterior lobe intact, normal parturition, followed by lactation, took place in 9 out of 10 animals; only one animal delivered late, on the morning of the 24th day. Rats in which the anterior lobe only had been removed on the 12th day behaved in general as did the completely hypophysectomized rats. From a group of 12 such animals 3 had a normal parturition, while in 9 pregnancy and parturition were abnormal. The same ratio existed among rats from which the total pituitary had been removed, 4 out of 16 delivering normally. No difference could be detected

[§] Mortality after hypophysectomy is higher in adult, pregnant rats than in immature rats. (In rats hypophysectomized at 26-28 days of age the mortality in the first 10 days post-operative is nearer 6% and is reduced to practically zero after comparable treatment with terramycin.) In these experiments where adults were used it was not possible to select as carefully the animals to be hypophysectomized due to the more limited number from which to choose; also the operative procedure required more time than in younger animals with thinner bony plates. The operations where special lobes were removed also required more care.

histologically between the endocrine organs of rats which delivered normally and those in which the duration of pregnancy and parturition were abnormal.

Discussion. There are certain differences between these results and those previously reported in the literature on the effect of the pituitary on parturition, as shown by its removal. Some animals from which either the complete hypophysis or the anterior lobe were removed, littered with slight or no delay and gave birth to living young. In animals which had not yet delivered on the 26th day after conception, no living young were born or were found alive *in utero* at autopsy. Typically, at this late period, the young were macerated and the uterus was filled with blood; resorption of some of the dead fetuses had begun. Teel(5) found that in prolonged pregnancy induced in intact rats by administration of pituitary extracts, living young could be removed from the uterus on the 25th day but that all fetuses were dead by the 26th day. Selye, *et al.*(3) reported that hypophysectomized rats gave birth to living young as late as the 26th day. It is possible that the use of different strains of rats, or of a different method of designating day 1 of pregnancy may be responsible for this difference in results. Pencharz and Long (1,2) reported that pregnancy was prolonged and that the animals died without giving birth following hypophysectomy on the 11th to 20th day of pregnancy. In the studies here reported parturition was normal in some of the rats.

Terramycin injections given post-operatively not only reduced the fatality rate after the operation, but also unexpectedly increased the number of normal births. Furthermore, among animals with abnormally prolonged pregnancy, the fatality during parturition was lower than it was in non-injected animals. Whereas Pencharz and Long(2) reported that 71% of 28 hypophysectomized animals died after unsuccessfully attempting to deliver, in this study deaths were recorded in only 7% of 30 animals treated with terramycin, and in 37% of 27 non-injected animals.

Ablation of the posterior lobe, either before pregnancy or on the 12th day of pregnancy, did not interfere with normal gestation parturition, or onset of lactation. It may be claimed

that the infundibular stalk and the tuber cinereum were left intact and thus enough of the neurophophysis remained to secrete amounts of oxytocin sufficient for normal parturition. These parts of the neurophophysis, however, also remained when complete hypophysectomy was performed, yet delivery was abnormal in most cases. Furthermore, removal of the anterior lobe was followed by deranged parturition even though the posterior lobe as well as the stalk was left intact. These findings, then, confirm the previous observations that the posterior lobe is not essential for parturition in the rat.

The effects on parturition of removal of the anterior lobe were the same as those which were caused by total hypophysectomy. In both cases, most of the animals (75%) delivered late, failed to deliver and began to resorb the fetuses, or died. It seems convincing that the derangement in the birth mechanism occurring after total hypophysectomy is due to the removal of the anterior lobe. It is not known, however, whether this essentiality of the anterior lobe is due to a direct or an indirect influence on the process of parturition. A direct action is not conclusively proven, and there are indications that metabolic or other factors indirectly related to anterior pituitary function are involved. The fact that some animals in each experimental group delivered normally, and also the variation in the severity of the derangement in the animals delivering abnormally, indicates that a multiplicity of factors influence parturition. Among the factors which may interfere with the process are the state of health of the animals, derangement in carbohydrate metabolism, decreased food consumption, weight of the fetuses, and the persistence of corpus luteum function.

The general health of the animals may be of great importance in determining the ability to expel the fetus. Hypophysectomized animals are very susceptible to respiratory infections. Many of the animals which failed to deliver normally had pulmonary lesions, though this was not limited to them alone. The finding that terramycin injections following hypophysectomy reduced not only the post-operative fatalities but also the fatalities during parturition, and resulted in a higher rate

of normal deliveries, may be explained in part as due to reduction of pulmonary infections. After hypophysectomy the carbohydrate metabolism of rats is well known to be deranged. Though it is adequate for life under favorable conditions there is small margin for meeting adverse conditions. Such animals while attempting to deliver may soon exhaust their glycogen supply and pass into a hypoglycemic shock, dying if parturition is prolonged. The food consumption is less than normal in pregnant hypophysectomized rats(6). In these animals, which are already susceptible to hypoglycemia, the decreased food intake may further contribute to the exhaustion, failure to give birth at term, and eventual death.

The weight of the fetuses on the 21st day of pregnancy in hypophysectomized rats is reported to be the same as or smaller than the weight of fetuses from normal rats(6,7). The size of the fetuses would then not be a primary factor in preventing parturition at term. However, when parturition is delayed, the size of the fetuses may continue to increase which may then secondarily cause difficulties in late delivery. No direct evidence is available regarding this point in hypophysectomized rats. One can only reason from normal pregnant rats in which the fetuses become larger than normal young at term when gestation is prolonged by injections of anterior lobe or luteal extracts. (5,8).

That the corpora lutea of hypophysectomized pregnant rats continue to function is suggested by their morphology. Pencharz and Long(2) noted that the corpora lutea were indistinguishable from those in normal rats at the same day of pregnancy. Further, it was observed in the course of this study that at autopsy on the 26th day the corpora lutea of rats hypophysectomized on day 12 were larger than those of normal post-partum rats. This suggests the continued secretion of a luteotrophic factor, which, in the absence of the pituitary, must have been provided by the placenta. Astwood and Greep(9) have

demonstrated such a luteotrophic factor in placental tissue.

Another mechanism involved in the prolonged life of the corpora lutea which must not be overlooked is the possible removal with the pituitary of a corporolytic factor(10) which in the normal animal would act to diminish corpus luteum function. This subject has not yet received sufficient attention.

Summary. 1. Ablation of posterior and intermediate lobes of the hypophysis either before conception, or on 12th day of gestation resulted in no disturbances in duration of pregnancy, in parturition or in onset of lactation. 2. Removal of anterior lobe of the hypophysis had the same effects on pregnancy and parturition as did total hypophysectomy. After both types of operation 25% of the rats delivered normally at term; 75% had a prolonged pregnancy (1 to 3 days) and either delivered late, resorbed, or died in an effort to deliver. 3. Terramycin injections given on the first and second days following hypophysectomy, decreased post-operative mortality, resulted in a larger percentage of normal deliveries, and in a smaller fatality rate at parturition as compared with non-injected animals.

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Received November 16, 1953. P.S.E.B.M., 1953, v84.