2. Moore, A., Wroblewski, F. Presented at 7th Internat. Cancer Congress, London, July 7, 1958.

3. Mawson, C. A., Fischer, M. I., *Biochem. J.*, 1953, v55, 696.

4. Hotchkiss, R. S., *Fertility in Men*, J. B. Lippincott, Philadelphia, 1944.

5. MacLeod, J., Hotchkiss, R. S., *J. Urol.*, 1942, v48, 225.

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Essential Role of Hypophysis in Hypercorticism and Hyperovarianism in DBA x CE and Reciprocal Mice.* (24318)

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In a number of inbred strains of mice (DBA (1), CE(2), A, C_{57}BL and C_3H(3)) and in some of their hybrid offspring (C_3H x A(4), DBA x CE(5)) adrenal cortical hyperplasia and/or adenocarcinoma develop in both sexes subsequent to early gonadectomy. Similar adrenal tumors develop in intact NH mice due to spontaneous failure of the gonads at about 9 to 10 months of age(6). That these cortical tumors are endocrinologically active is evidenced by their growth-stimulating effect on the atrophied reproductive organs after they develop in the gonadectomized mice. In some instances the growth induced may become hyperplastic in nature. Hyperplasia of the reproductive tract also occurs in intact DBA x CE and reciprocal hybrid female mice due to spontaneous hyperovarianism that begins to manifest itself at 6 to 7 months of age and which persists throughout the life of the animals(7).

It has been the general consensus of the several authors cited that the hypophysis is involved in both spontaneous and induced adrenal and ovarian endocrinopathies. No direct evidence, however, has been offered in support of this contention. The following experiments were designed to determine whether or not the hypophysis is essential to development of hyperovarianism in intact mice and to development of hypercorticism in neonatally ovariectomized mice.

Procedure. The present study was begun with 82 virgin female DBA x CE and reciprocal hybrid mice, born in the Jackson Laboratory colony and maintained at 70°F and on a diet of Purina laboratory chow and water *ad libitum*. The mice were divided into 4 groups: (1) 24 received no treatment, (2) 8 were ovariectomized within 72 hours after birth, (3) 25 were hypophysectomized at weaning, *i.e.* at approximately 30 days of age,‡ and 25 were ovariectomized shortly after birth and were then hypophysectomized at weaning. The operated animals were weighed occasionally but were subjected to no other treatment.

The mice were sacrificed at from 6 to 9 months of age, the earliest period during which hyperplasia of the ovaries, adrenals and uterus is consistently present in intact animals. Whereas all the operated animals survived the immediate post-surgical period, there was a high delayed mortality rate among the hypophysectomized mice, particularly at from 60 to 90 days of age. Several of the surviving hypophysectomized mice, although much lighter in weight than the intact animals, gained 4 to 5 g and consequently were eliminated from the study because of incomplete removal of the gland. Hence, there were but 5 completely hypophysectomized and 10 hypophysectomized-ovariectomized mice that survived at least to the required age

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TABLE I. Quantitative Effects of Hypophysectomy on Hypercorticism and Hyperovarianism in DBA × CE and Reciprocal Mice.

Treatment	Age, mo	No. of mice	Body wt, g	Organ wt, mg/100 g body wt			
				Hyp	Adrs	Ovaries	Uterus
None	6-7	12	25.7 ± 3.6*	7.8	21.9	85.3	438.4
	8-9	12	25.9 ± 1.1	7.9	22.1	143.4	558.7
Ovariectomized at birth	8-9	8	34.4 ± 2.0	7.8	27.7	—	99.1
Hypophysectomized at weaning	6-9	5	12.5 ± .5	—	14.9	18.5	40.0
Ovariectomized at birth and hypophysectomized at weaning	6-9	10	13.4 ± .4	—	14.1	—	20.1

* ± S.E.

of 6 months. The animals were autopsied immediately after sacrifice and weights of adrenals, uteri, hypophyses and/or ovaries, if present, were determined to the nearest 0.1 mg on a Roller-Smith torsion balance.

In the neonatally ovariectomized mice there is an increase of approximately 30% in body weight and both an absolute and relative increase in adrenal weight of about the same magnitude as compared with body and adrenal weights in the intact animals of the same age. The uteri in the 8- to 9-month-old castrates do not show the hyperplasia present in the intact mice, but in comparison with the uteri in the hypophysectomized groups, it is evident that in these animals some degree of uterine growth has occurred in conjunction with enlargement of the adrenals. In the hypophysectomized intact and ovariectomized mice, on the other hand, there is little doubt that there is marked failure of ovarian and adrenal growth and absence of uterine stimulation by these organs. The results are summarized in Table I.

Discussion. The present observations on weights of adrenals, ovaries and uteri in 8- to 9-month-old intact and neonatally ovariectomized DBA x CE and reciprocal hybrid mice confirm quantitatively what previously has been described primarily in morphological terms. Whereas the degree of adrenal and uterine enlargement in the 8- to 9-month-old castrates is but a fraction of that which develops after 12 months, selection of this earlier stage in the hypercortical syndrome was necessary due to the difficulty of maintaining the hypophysectomized mice to more advanced ages.

It has been postulated, principally on the basis of theoretical considerations, that adrenal hyperplasia and subsequent cortical tumors that develop in gonadectomized mice of the several strains previously mentioned are the result of stimulation of the adrenals by elevated titers of hypophyseal gonadtropins resulting from removal of the gonads(3). No such formal hypothesis has been offered to explain the hyperovarianism exhibited by intact mice, but the implication of the hypophysis has been assumed explicitly(5,8). The present observations cannot provide a detailed theory of the physiological mechanisms involved in the pathogenesis of the adrenal and ovarian endocrinopathies in these mice, but the data do provide indisputable direct evidence of the essential role of the hypophysis in their development.

Summary. Weights of the adrenals, ovaries, uteri and hypophyses of 6- to 9-month-old DBA x CE and reciprocal hybrid mice were measured in: (1) intact virgins, (2) neonatal castrates, (3) mice hypophysectomized at weaning, and (4) hypophysectomized castrates. There was marked reduction in size of the adrenals, ovaries and uteri in the hypophysectomized intact animals and of adrenals and uteri in the hypophysectomized castrates. Since at 6 to 9 months of age intact mice of these hybrid strains exhibit spontaneous enlargement of ovaries and hyperplasia of the reproductive tract, and animals ovariectomized neonatally exhibit hyperplasia of adrenals and hormonal stimulation of the reproductive tract, the present data provide definitive evidence of the essential role of the hypophysis in these hypercortical and hyperovarian syndromes.

1. Fekete, E., Woolley, G. W., Little, C. C., *J. Exp. Med.,* 1941, v74, 1.
2. Woolley, G. W., Little, C. C., *Cancer Research,* 1945, v5, 193.
3. Dickie, M. M., Woolley, G. W., *ibid.,* 1949, v9, 372.
4. Smith, F. W., *ibid.,* 1948, v8, 641.
5. Christy, N. P., Dickie, M. M., Atkinson, W. B., Woolley, G. W., *ibid.,* 1951, v11, 413.
6. Frantz, M., Kirschbaum, A., Casas, C., PROC. SOC. EXP. BIOL. AND MED., 1947, v66, 645.
7. Dickie, M. M., Atkinson, W. B., Fekete, E., *Anat. Rec.,* 1957, v127, 187.
8. Atkinson, W. B., Dickie, M. M., Fekete, E., *Endocrinol.,* 1954, v55, 316.

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Effect of Behavior on Development of Resistance in Trichinosis.* (24319)

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In recent years the effect of external conditions on resistance to a pathogen has received increasing attention. This paper describes the effect of behavior upon resistance to *Trichinella spiralis* infections in mice. A series of papers(1,2,3,6) has demonstrated that crowding in mice produces hypertrophy of the adrenal glands and a chain of physiological consequences, especially with respect to reproductive functions. In addition it seemed probable that these adrenal changes would affect resistance. Resistance here is defined as response of a host to past or present experience with a parasitic organism or a chemically related entity, whereas the term insusceptibility is restricted to the properties of a host which render it unsuitable as a habitat for a parasite but which do not represent a response of the host to the parasite(11). This paper presents the first of a series of studies designed to determine alterations of development of resistance in respect to density of the population. The parasite *Trichinella spiralis* was selected because considerable information was available on the mechanisms of resistance and because it was possible to set up an experiment in which transmission from mouse to mouse did not occur(7). It has been shown that during the initial phase of a *Trichinella* infection there is an inflammatory response in the wall of the gut. This response is thought to be involved in determining length of life of the adult worms(9). It has been known for several years that resistance to *Trichinella* is altered by cortisone treatment(10,12). Coker(4,5) showed that when mice are given injections of cortisone the intestinal inflammation in trichinosis is reduced. As a consequence, the life of the adult worms is prolonged and more larvae are presumably deposited in the host's tissues than is the case in hosts not receiving cortisone treatment. Resistance to certain other animal parasites is altered by administration of cortisone to the host(13).

Methods. The general method consisted of infecting mice with *Trichinella,* then arranging part of the mice as a group to contrast the effects of interaction of individuals with the condition of isolation. The mice are called wild strain because they are raised in large cages from mice that are regularly replaced by mice caught in the wild. These mice have been used for a variety of studies of the adrenals(1,6). The young mice are weaned at 20 days and placed in jars separated from each other by partitions so that one mouse cannot see another mouse. Food and water are provided and the mice live in these jars until they are sexually mature at an age of about 4 months. Only male mice are used in these studies.

The grouping procedure consists of placing 6 mice together in a large can for about 4 hours a day. At the end of this time each mouse is put back in his own jar which is kept isolated from other mice. The large can does not have food or water. The mice begin

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