

THE DIFFERENTIAL EFFECT OF HEREDITARY MOUSE DWARFISM ON THE ANTERIOR- PITUITARY HORMONES¹

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TWO FIGURES

In an earlier paper we have pointed out the similarity of the conditions found in the hereditary dwarf mouse of the Silver strain and in hypophysectomized rats (Smith and MacDowell, '30). In both instances growth is either absent or much below normal and the thyroids and adrenals are markedly imperfect. Implants with fresh anterior hypophysis restore these animals to a nearly normal condition. The outstanding point of difference between these dwarf mice and hypophysectomized rats lies in the degree of development of the reproductive system.

The testes of dwarfs are firm and, though small, have the characteristic shape and appearance of normal testes. The seminal vesicles and other accessory glands are well developed. In section all generations of sperm-forming cells are seen. Sperm, though apparently not as numerous as in the testes of normal adults, nevertheless are present in many tubules. They are present in the epididymis and vas deferens in numbers approaching normal (fig. 1). Tests carried out on two living dwarfs have revealed motility of these sperm equal to that in normals. On the other hand, in hypophysectomized animals, the testes become flabby, sperm do not

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develop, and the seminal vesicles and other glands become greatly reduced in size.

The reproductive system of the female dwarf does not reach as advanced a stage of development as the male. Follicles with cavity formation are rare; the uterus is infantile. In only extremely rare cases has the vaginal orifice become established and the spontaneous opening in these cases is made uncertain by the possibility of the opening having been

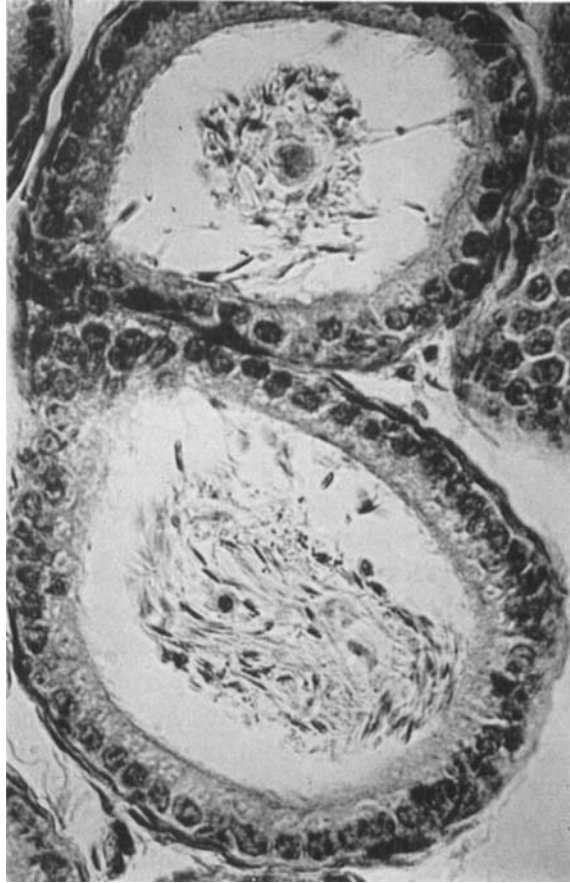


Fig.1 Photomicrograph of tubules in epididymis of a dwarf male, showing the numerous sperm characteristically present. Age of mouse, 198 days; weight, 8.7 grams. $\times 630$.

effected by trauma. Nevertheless, the ovaries of hypophysectomized rats show even less activity; the follicular atresia sets in before the stage of cavity formation and the ovary becomes filled with interstitial tissue. The uterus becomes thread-like. Thus the reproductive system of the male dwarf, and to a lesser extent the female, contrasts with that in animals in which the anterior hypophysis is completely lacking. This difference, together with the suspicious finding that, although the definitive eosinophils of the dwarf anterior lobe were certainly lacking, no statement could be made as to the basophils, suggested that the defect of the dwarf anterior lobe might involve the suppression of the growth hormone without a corresponding suppression of the gonad-stimulating hormone. Accordingly, separate biological tests for the presence (or absence) of these two hormones in the dwarf pituitaries have been made.

THE GONAD-STIMULATING HORMONE

The most sensitive biological test available for the presence of the gonad-stimulating hormone appears to be the response of the reproductive organs of normal, immature female mice. Normal Bagg albino mice, twenty days of age and approximately the same weight, were treated by intramuscular implantations of fresh pituitaries from dwarfs. In the first experiment four recipients from the same litter were used; into one the pituitaries from two dwarfs were implanted on the first day and two more on the second day. Into another the pituitary from a normal young female mouse was implanted on the first day, with no further treatment. The other two mice served as untreated controls. On the third day the vaginal orifices of the two treated females were established, while the two controls were still closed on the fourth day. The autopsies made on the fourth day showed the uteri of the two treated females engorged with fluid and weighing (drained of fluid) more than three times the uteri of the controls. The ovaries of the mouse treated with a single normal mouse pituitary were slightly heavier than the con-

trols; the ovaries of the mouse treated with the dwarf pituitaries were markedly heavier (over $2\times$).

In the second experiment this test was repeated with a similar group of four normal, immature, litter mates, with the modification that the sex of the dwarf donor was taken into account. One female was the recipient of four pituitaries from female dwarfs; another, of four pituitaries from male dwarfs; one, of a single normal female pituitary, as before, and one was untreated. On the fourth day, the conditions of the vagina and uterus as well as the organ weights completely confirm the results of the first experiment and indicate further that the pituitaries of male and female dwarfs are equally effective. Again, the single implant of a normal pituitary, although effective, is less powerful than the four dwarf glands.

In the third experiment the anterior lobes of four dwarf glands were given to one normal female, and the posterior lobes to another (two per day for two days); to another was given a whole normal pituitary on the first day and also on the second day; the fourth female was held as control. On the fourth day, the results of the implants with dwarf anterior lobe agreed with the previous findings for the whole dwarf gland. The mouse given the dwarf posterior lobes showed no difference from the control; the ovaries and uterus of the mouse receiving the two normal glands and the one receiving the four dwarf anterior lobes were almost identical.

The results for each experiment are summarized in the table. Each of the four normal females that received anterior lobes from dwarfs showed a pronounced and unquestionable ovarian and uterine response. This statement is based on the comparison with four untreated controls and one treated with posterior lobes. Eliminating the slight differences in body weight in the different experiments by reducing the organ weights to a percentage basis, the following averages are obtained: ovaries: controls, 0.034 per cent; dwarf-implanted, 0.091 per cent; uteri: controls, 0.107 per cent; dwarf-implanted, 0.563 per cent.

Implants of hypophyses from dwarf and normal mice into immature female mice

EXPERIMENT	DONORS			IMPLANTS			RECIPIENTS						
	Type	Number and sex	Combined body weights, grams	Lobes of hypophysis	Number of glands		Pedigree no.	Weight (20 days old), 1st day	Vaginal opening, day	Autopsy on fourth day			
					1st day	2nd day				Uterus	Body	Ovaries	Uterus ¹
I	Dwarf	3♀s, 1♂	29.3	Anterior and posterior	2	2	77112	9.5	3rd	Engorged	11.0	.0106	.0486
	Normal	1♀	20.0	Anterior and posterior	1	0	77114	9.5	3rd	Engorged	11.7	.0055	.0512
II		None			0	0	77113	9.5	Closed	Infantile	10.7	.0042	.0151
		None			0	0	77115	10.0	Closed	Infantile	11.5	.0040	.0122
	Dwarf	4♀s	27.6	Anterior and posterior	2	2	77528	8.15	4th	Engorged	9.6	.0085	.0622
	Dwarf	4♂s	26.3	Anterior and posterior	2	2	77529	8.05	3rd (minute)	Engorged	9.4	.0080	.0654
III	Normal	1♀	17.0	Anterior and posterior	1	0	77530	7.75	4th (small)	Slightly swollen	9.0	.0039	.0172
		None			0	0	77527	8.55	Closed	Infantile	9.6	.0028	.0068
	Dwarf	4♀s	30.4	Anterior	2	2	77924	9.10	3rd	Engorged	11.12	.0106	.0597
	Normal	2♀s	31.5	Posterior	2	2	77923	9.10	Closed	Infantile	9.78	.0033	.0102
				Anterior and posterior	1	1	77921	9.05	3rd	Engorged	11.45	.0106	.0461
		None			0	0	77922	9.45	Closed	Infantile	9.95	.0035	.0116

¹ Fluid removed before weighing.

Four dwarf anterior lobes appear to be considerably more potent than a single normal gland. They about equal in potency two normal glands. Although in each case the number of dwarf glands implanted was greater, nevertheless the dwarf glands were so small that the amount of dwarf anterior-pituitary tissue was obviously less than the amount of normal anterior-lobe tissue used. Consequently, it appears that in a unit quantity of the anterior pituitaries of the dwarfs there is a greater concentration of the gonad-stimulating hormone than in the normal mature female mouse.

The difference between the condition of the reproductive system in the dwarfs and in hypophysectomized rats is interpreted as a result of the formation of the gonad-stimulating hormone in the anterior lobes of the dwarfs and its liberation into the circulation.

Although the male dwarf shows a more advanced development of the reproductive system than the female, it is of interest to note that the biological tests show no sex difference in the concentration of the gonad-stimulating hormone.

THE HORMONE STIMULATING GENERAL BODY GROWTH

If the gonad-stimulating hormone can be present in the anterior pituitaries of dwarfs in considerable concentration without expressing itself in sexual maturity, it seemed possible that the growth hormone in reduced amounts might also be present. Although the persistence of the dwarf condition throughout life speaks against such a supposition, the point seemed open to study. Accordingly, dwarf pituitaries were tested biologically for the presence of the growth hormone. For this test dwarfs were used as recipients, since the unique sensitiveness of their growth response to normal pituitary transplants gives them great value in testing for small amounts of this hormone. While the gonad-stimulating hormone per gland (not per unit weight of tissue) in the dwarfs stands in relation to normal approximately as 1:2, the relative amount of the growth hormone, if present at all, must from the following experiment be considerably less.

A 7-gram male dwarf, three months old, was given eleven daily implantations of dwarf pituitaries. Two glands were given at each implantation. Treatments were omitted on the fourth and eleventh days of the experiment, so that the eleventh treatment was given on the fourteenth day. A dwarf brother of the above mouse, of approximately the same weight, was given one normal pituitary from a young adult mouse on each of the days the first dwarf was treated. The implants of the dwarf glands showed absolutely no effect

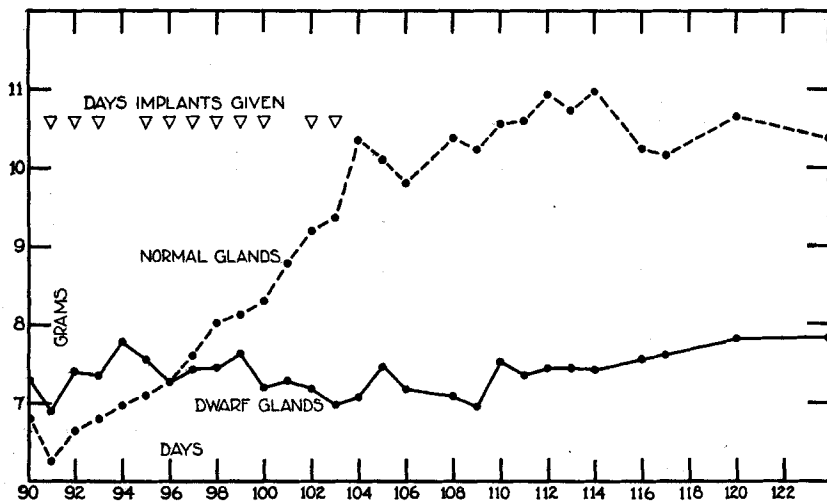


Fig. 2 Growth curves of dwarf mice receiving implants of fresh hypophyses of normal mice (broken line) and of dwarf mice (solid line).

(fig. 2). The rise of the curve on the first three days is not significant, since in most cases in which normal glands are used the first few days show no response. During the rest of the period of treatment the general tendency is downward, so that the weights at the end and at the beginning are alike. On the other hand, the response to the normal implants was marked—an accelerating rise of over 3 grams—followed by an abrupt break at the end of the treatments. Three weeks after the end of the implantations, the dwarf that was given the dwarf glands again rose a little above 7.5 grams, while

the other dwarf, after a gradual rise for ten days after the end of the experiment, ranged between 10 and 10.5 grams during the next ten days.

While this experiment cannot be considered to prove the complete absence of the growth hormone in the pituitaries of dwarfs, since it is clearly possible that larger numbers of glands at each treatment and a prolongation of the treatments might cause some response, it serves to demonstrate that the reinforcement of the dwarf's own anterior lobe by two other dwarf glands per day is still insufficient to even start the growth processes in an animal that for two and a half months has remained infantile in size and whose dwarf litter mate grew strikingly when implants of minute amounts of normal anterior pituitary were made.

The results thus show a high concentration of the gonad-stimulating factor in the anterior pituitaries of the dwarfs, whereas the growth-stimulating factor is not present in sufficient amounts to be detectable with the sensitive test form used. These findings correspond strikingly to the conditions found in the dwarfs, for the deficiency in general body growth is much more pronounced than is that displayed by the reproductive organs.

It is well known that in man a neoplasm may differentially suppress one or all of the hormones of the anterior pituitary. In the dwarf mice, instead of a neoplasm, the hereditary constitution leads to a differential suppression of the growth-stimulating hormone.

SUMMARY

The reproductive system of dwarf mice, especially in males, is further developed than in hypophysectomized rats, whereas other disabilities are similar in the two types. This suggested that the pituitary growth hormone in the dwarf might be suppressed without a corresponding suppression of the gonad-stimulating hormone.

Biological tests for the presence (or absence) of these two hormones show that such is the case. There is a high con-

centration of the gonad-stimulating hormone in the pituitaries of dwarfs as revealed by implants, whereas the growth hormone is not present in a sufficient amount to have been detected even with the sensitive test form used. These findings are correlated with the disabilities exhibited by the dwarfs.

LITERATURE CITED

- SMITH, P. E., AND E. C. MACDOWELL 1930 An hereditary anterior-pituitary deficiency in the mouse. *Anat. Rec.*, vol. 46, pp. 249-257.