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6. This research was supported in part by a grant from the Central Ohio Heart Association.

10 November 1959

Primary Site of Gene Action in Anterior Pituitary Dwarf Mice

Abstract. The transplantation of anterior pituitary glands of normal mice into hypophysectomized dwarf littermates has resulted in mice that are normal in appearance and growth rate. In contrast, the anterior pituitary gland of dwarf animals, when placed in the sella of hypophysectomized normal littermates, failed to promote the growth of these animals. These results indicate that the primary site of gene action in dwarfism lies in the anterior pituitary itself rather than in the hypothalamus.

The dwarf mouse has been used extensively in a variety of endocrine studies. Snell (*1*) demonstrated that the dwarfism is the result of a single recessive gene that is not sex-linked. The immediate cause of dwarfism is the failure of the anterior pituitary gland to function in the production of growth hormone. Smith and MacDowell (*2*) were the first to suggest this cause after observing the hypoplastic nature of the anterior pituitary lobe, the sexual glands, and the adrenal cortex. These two investigators produced dwarf mice that were normal in growth and appearance following daily implants of normal rat pituitaries. Kemp and Marx (*3*) demonstrated normal growth and appearance of dwarf mice following daily injections of anterior pituitary extracts. Francis (*4*) studied the cytology of the pituitary of the hereditary dwarf in some detail and confirmed earlier studies which related the dwarfism to an absence of typical acidophiles and a deficiency of growth hormone. Current interest in hypothalamic-anterior pituitary interrelationships directed our attention to the possibility that the primary site of gene action might lie in the hypothalamus rather than in the anterior pituitary per se.

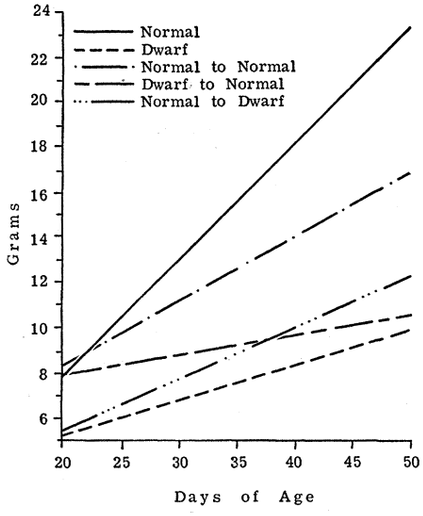

Fig. 1. Growth curves of intact and pituitary graft-bearing mice of the genetic dwarf strain. Each curve represents pooled data obtained from a group of five animals.

In order to answer this question we have transplanted anterior pituitary glands between normal and dwarf members of litters whose parents were heterozygous for the dwarf gene. Our experiments were so designed that the activity of the anterior pituitary homografts could be observed by daily weighings and resultant growth curves. Using littermates, we hypophysectomized normal mice (14 to 18 days old) by the parapharyngeal method. A dwarf littermate of like sex was killed, and its pituitary was placed immediately into the sella of the hypophysectomized normal littermate. The transplanted pituitaries were held in place against the hypothalamus by Gelfoam sponge (Upjohn), and the incision was closed with silk sutures. In this manner, transplants were made from dwarf mice to normal mice, from normal mice to dwarf mice, and from normal mice to normal mice. There were five animals in each of these groups. The growth of these animals and that of five unoperated dwarf and five unoperated normal mice was determined by daily weighings for a 30-day period (20th day through the 50th day). Growth curves representing these five groups of mice were then made.

Our observations were as follows (Fig. 1). (i) Unoperated normal mice gained 15.5 gm. (ii) Unoperated dwarf mice gained 4.4 gm. (iii) Hypophysectomized normal mice bearing transplants from normal mice gained 8.7 gm. (iv) Hypophysectomized normal mice bearing transplants from dwarf mice gained 2.8 gm. (v) Hypophysectomized dwarf mice bearing transplants from normal mice gained 6.7 gm.

More important than the total weight gain is the rate of weight gain. The rate of weight gain in hypophysectomized dwarf mice bearing pituitaries of normal mice was almost equal to the rate of growth of hypophysectomized normal mice bearing pituitary transplants from normal mice. On the other hand, the rate of weight gain of hypophysectomized normal mice bearing pituitaries of dwarf mice was even less than the rate of growth of unoperated dwarf mice.

These results indicate that the hypothalamus of the hereditary dwarf mouse is capable of stimulating a pituitary graft from a normal animal to function at a level comparable to that seen in normal animals bearing similar pituitary grafts. It is noteworthy that the dwarf mouse, when given a normal anterior pituitary as an intrasellar graft, comes to resemble a normal mouse in rate of growth and in physical appearance. Also, the evidence obtained indicates that the pituitary of the dwarf mouse is incapable of producing significant amounts of growth hormone, even when it is placed in contact with the hypothalamus of a normal animal. This shows rather clearly that the anterior lobe of the pituitary and not the hypothalamus is the primary site of gene action in the anterior pituitary dwarf mouse.

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5. This study was supported by grants 2R-29 and RG-4723 from the U.S. Public Health Service.

3 August 1959

Heterogeneity of Ion Exchange Resins

Abstract. The density gradient method of Linderström-Lang has been used to study density variations among swollen beads in batches of cation exchange resin. Solutions of salts such as sodium tungstate which have dense anions are used. Certain commercial resins appear to be very uniform in cross linking and sulfonation.

A report by Högfeldt (*1*) shows that individual beads in a batch of ion exchange resin can differ widely in their characteristics. Beads taken from a batch of sulfonated polystyrene resin with a nominal 4 percent of cross linking showed selectivities for silver ions against hydrogen ions which varied by a factor of more than 2. Parallel variations were found in the swelling. These could be due to differences in cross linking, sulfonation, or both.

In our laboratory we are studying the thermodynamics of ion exchange,

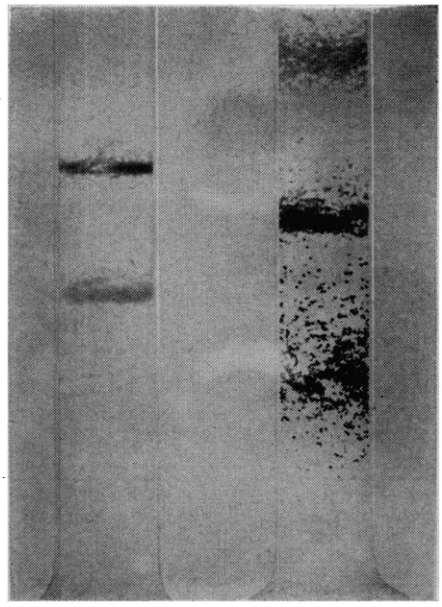

Fig. 1. Density gradient tubes with ion exchange resins in sodium tungstate solutions. (Left) Dowex 50-W. (Right) Laboratory preparations of sulfonated polystyrene resins.

and the homogeneity of the resins used is obviously very important. We have used the density gradient method of Linderström-Lang (*2*) to study this homogeneity. A tube was set up which had two bulbs, each of about 100-ml capacity, joined by a vertical tube 2.5 cm in diameter and 18 cm long. A solution of sodium tungstate which was dense enough to float the resins was poured into the lower bulb and the lower half of the vertical tube. Over this, filling the upper bulb, was poured a more dilute solution of sodium tungstate which was not dense enough to float the resins. The tube was set in a thermostat at 25° ± 0.01°C and left for 2 days. The solutions mixed by diffusion, and a stable gradient of concentration and density was established along the length of the vertical tube.

Small portions (about 50 mg) of the resins to be studied were then dropped into the tube. These were sulfonated polystyrene resins converted to the sodium form and air-dried. Within an hour they came to rest within the vertical tube, the more highly cross-linked resins settling further down the tube, and they remained in the same position for days.

Figure 1 is a photograph of two such tubes. On the left are two commercial resins supplied by the Dow Chemical Co. (Dowex 50-W, 50–100 mesh), with 4 and 8 percent cross linking, respectively; the 4-percent cross-linked resin is on top. As may be seen, these resins are remarkably uniform, though both contain a small amount of light material which floats just above the main quantity of resin. On the right are three laboratory-scale batches with nominal 7, 10, and 17 percent cross linking, respectively. These are less homogeneous.

To determine the density distributions in the vertical tubes, small portions of solution (0.2 to 0.5 ml) were withdrawn from measured levels by a pipet with a long capillary tip, and their densities were measured by a micropyknometer. Or, their refractive indices were measured and compared with those of solutions of known concentration and density. Typical data are given in Table 1.

Sodium tungstate (Na_2WO_4) was chosen as the heavy solute because it is the anion which is dense, and anions are partially excluded from a cation exchange resin. Another heavy solute which worked well was disodium lead ethylenediamine tetraacetate (Na_2PbY).

The density at which the resin floats is determined by its swelling, which in turn depends on two factors, cross linking and extent of sulfonation. The "laboratory batch" resins were somewhat lighter than the commercial resins of comparable cross linking, a finding which suggests that they were more highly sulfonated. That this was, in fact, the case is seen from the ion-exchange capacities reported in Table 1. A resin could appear homogeneous by the flotation test yet not be truly homogeneous; by using more than one flotation solute it may be possible to distinguish between the effects of cross linking and sulfonation.

The flotation technique has obvious potentialities for producing very uniform batches of resin (*3*).

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Table 1. Concentrations, densities, and refractive indices of solutions floating sulfonated polystyrene ion-exchange resins.

Resin		Na_2WO_4			Na_2PbY		
Cross-linking (%)	Exchange capacity*	Sp. gr. (25°C)	n^{25}_D	WO_3 (wt.%)	Sp. gr. (25°C)	n^{25}_D	Pb (wt.%)
			Dowex 50-W				
4	4.78	1.302	1.3688	28.0	1.298	1.3960	13.35
8	4.48	1.338	1.3718	30.65	1.333	1.4016	14.92
			Laboratory batches				
7	4.60	1.322	1.3701	28.2			
10	4.425	1.347	1.3728	31.55			
17		1.383	1.3768	35.0			

* Exchange capacities are in milliequivalents per gram of dry sodium resin.

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Zinc-65 in Cyclotron Workers

Abstract. Small but persistent body burdens of zinc-65 have been found in cyclotron workers. This radionuclide and others are produced by nuclear reactions with the construction materials of the cyclotron. Only zinc-65 has gained entry into the body, but in amounts of less than 1 percent of the maximum permissible amount.

Measurement of Los Alamos Scientific Laboratory cyclotron workers in November 1958 in the human counter (*1*), a large liquid scintillator designed for detection of radioactivity in human beings, revealed the presence of radioactivity in excess of normal potassium-40 activity in the 1- to 2-Mev region. This excess was identified as zinc-65 in the Los Alamos human spectrometer (*2*), a large NaI (T1) crystal in a steel room by means of which radioactivity in human beings can be characterized. Figure 1 is a typical spectrum showing the characteristic zinc-65 peak at 1.11 Mev in addition to the usual cesium-137 and potassium-40 peaks.

Zinc-65 can be produced in large quantities in cyclotrons accelerating deuterons by the reaction Cu^{65} (*d*, 2*n*)-Zn^{65} on copper dees and other parts. In fact, this reaction has been used for producing zinc-65 of high specific activity (*3*) for biological tracer work. In the acceleration of helium-3 ions, lesser amounts result from the reaction $Cu^{65}(He^3,H^3)Zn^{65}$, and in addition the reaction $C^{12}(He^3,2He^4)Be^7$ may occur if carbon (as graphite, oil, grease, and so on) is bombarded. Deuteron reactions on iron, chromium, and manganese can produce manganese-54, which also results from the *p*,*n* reaction on chromium-54. The properties of these radionuclides are summarized in Table 1. The Los Alamos variable-energy cyclotron is used to produce beams of protons (3.9 to 9 Mev), deuterons