Effect of Fasting on Blood Sugars in Hereditary Hypopituitary Dwarf Mice.* (19995)

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Snell(1) described, in a strain of mice, an hereditary dwarfism which behaved as a true Mendelian recessive. Since then many investigations have been carried out on dwarf mice which have shown interesting morphological and metabolic anomalies. Snell(1) described their thyroid deficiency and obtained restorative effects with a thyroid-stimulating extract, and Smith and MacDowell(2) showed that a hypoplastic condition existed in the acidophilic cells of the anterior pituitary lobe and in the sex glands, the skeleton, and the adrenal cortex. By transplantation of the anterior pituitary lobe tissue from rats to dwarf mice, normal growth could be achieved and other underdeveloped structures were restored to normal. Therefore, they concluded that this dwarfism was the result of an hereditary anterior pituitary deficiency. Kemp(3,4) showed that normal growth could be restored by replacement therapy with anterior pituitary extract and with growth hormone. MacDowell, Laanes, and Smith(5); Dawson(6); Osborn (7); Marshak(8); Boettiger and Osborn(9); Rouse and Osborn(10); Schonholz and Osborn(11); Haack(12); Mirand and Osborn (13); and other investigators have all reported observations related to the endocrine or morphological abnormalities of the hypopituitary dwarf mouse.

Since various endocrine glands and their extracts have been found to have an influence on metabolic processes, it was felt that the hereditary hypopituitary dwarf might serve as an excellent animal in which to study blood glucose values associated with fasting.

Materials and methods. The animals used in this study were hereditary hypopituitary dwarf mice of the Bar Harbor strain, and for controls normal mice of the same strain were utilized. All dwarfs were 9 to 12 months old, ranging in weight from 9 to 14 g. Normal mice, 35 to 42 days old, served as controls, since their weights at this time were similar to the dwarfs, moreover, at this age the normal mice are developmentally similar to the dwarfs. The animals, bedded with ground corn stalks in solid-bottomed cages, were maintained on water and Purina laboratory chow. The temperature of the animal room was about 75°F. Experiments designed to determine the effects of fasting and nonfasting upon the blood sugar level of normal and of dwarf mice were carried out. The fasting periods used ranged from 12 to 96 hours, as indicated in the accompanying tables. Blood samples for sugar determinations were drawn after 10 p.m. While being bled, the mice were held gently to minimize the possible effect of excitement upon the blood sugar level. Blood for all sugar analyses (modified Folin-Wu methods of Klendehoj-Hubbard) was obtained by using the following technic. The animal's tail, having been stroked and warmed to promote vascular dilation and blood flow, was nicked with a sharp razor. If cut properly to include a prominent subcutaneous blood vessel, large drops of blood quickly form but the tail will heal promptly. Fresh blood was quickly drawn in a Sahli pipette and any excess wiped off the stem. The blood was then chemically prepared and the colors compared in a Klett colorimeter. The blood sugar values obtained are consistent relative amounts rather than absolute ones.

Results. Blood sugar determinations on fed and fasted dwarf and normal mice. In Tables I and II are shown the average blood glucose values for fed dwarf mice with normal controls and for dwarfs and normals fasted 12 to 96 hours. In the fed state the average

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TABLE I. Effect of Fasting on Blood Sugar of Normal and Dwarf Mice.

Normal				Dwarf				
No. in series	Hr fasted	Blood sugar, mg %	S.E.	No. in series	Hr fasted	Blood sugar, mg %	S.E.	t-value
10	0	155	± 4.26	21	0	143	± 4.96	.18*
50	12	147	± 2.21	15	12	110	± 3.13	10
18	15	128	± 2.23	10	15	105	± 2.81	6.38
37	16	123	± 1.82	15	16	100	± 4.56	6.21
28	18	119	± 2.21	15	18	94	± 4.35	5.10
18	21	124	± 2.47	10	21	95	± 3.98	6.17
50	24	133	± 2.18	15	24	93	± 2.98	10.81
12	27	131	± 2.56	15	27	97	± 1.82	12.50
30	30	137	± 2.23	15	30	92	± 5.08	8.03
24	40	138	± 3.36	15	40	88	± 2.68	11.36
12	48	117	± 1.23	12	48	75	± 1.71	21
12	72	112	± 1.44	12	72	71	± 1.87	17.91
12	96	103	± 1.03	12	96	68	± 1.86	15.90

* Not significant; all other values are significant.

TABLE II. Sequential Blood Sugar Determinations of 10 Normal and 10 Dwarf Mice Subjected to Fasting.

Hr fasted	Normal Blood sugar, mg %	S.E.	Dwarf Blood sugar, mg %	S.E.	t-value
*0	155	± 4.3	143	± 5	.18†
12	149	± 2.2	108	± 2.1	13.66
15	126	± 3.1	102	± 1.8	6.66
18	125	± 5.2	97	± 1.9	5.09
24	130	± 1.2	92	± 2.2	11.51
25	129	± 3.1	95	± 1.5	9.71
26	134	± 1.8	91	± 2	16.54
27	133	± 2.1	88	± 1.6	17.30
28	135	± 1.4	90	± 1.6	20.45
29	133	± 2.5	89	± 1.2	15.71
30	138	± 1.3	92	± 3.3	12.22
36	131	± 2.7	87	± 2.5	11.89
40	128	± 2.9	85	± 3.6	8.69

* Control mice.
† Not significant; all other values are significant.

blood sugar values for the dwarf mice (143 mg %) are slightly, but not significantly, lower than those of the normal mice (155 mg %). The blood sugar level of the fasting dwarf drops most precipitously around the 18th hour, followed by a more gradual but steady decline to an average value of 68 mg % after 96 hours of fasting. In contrast, normal mice exhibit the greatest blood sugar drop between the 12th and 18th hours of fasting, followed by some recovery between the 21st and 40th hours of fasting. Thereafter, a gradual second drop occurs, reaching a minimum of 103 mg % at the 96th hour. It is to be emphasized that, although prefasting blood sugar values are essentially alike for dwarfs and normal controls, the normal mice are able to maintain high levels rather tenaciously even during fasting, while dwarfs exhaust their blood sugars steadily and rapidly.

Table II presents the average blood sugar values from sequential blood sugar determinations on 10 normal and 10 dwarf mice subjected to fasting for 12 to 40 hours. Sequential determinations represent blood sugar analyses on a series of blood samples taken from the same mouse at intervals indicated during the fasting. These data are in close agreement with the results in Table I, despite the difference in sampling. It is clear, therefore, that dependable values may be obtained when multiple blood samples are taken from the same animal. These findings show the sensitiveness of the dwarf to fasting to a degree that the dwarf symptoms resemble the observations of others reported for hypophysectomized animals. Although in the dwarf a progressive decrease in the blood sugar level occurs, this decline is not associated with hypoglycemic convulsions and death, contrasted with hypophysectomized animals which may succumb if fasted for only 24 hours(14). In the fasting dwarf, activity is curtailed progressively until, by the end of the 96-hour fast, the dwarfs are either extremely lethargic or dead. In this study about one-third of the dwarfs expired by the 96th hour despite efforts to elevate the blood sugar by administering 5% glucose by stomach tube.

Starvation effects were not superficially discernible in normal mice at the end of the 96-hour fast.

Discussion. When hypophysectomized animals are fasted, they suffer unusually rapid losses of body carbohydrates. As seen in this study, the dwarf mice behave somewhat like hypophysectomized animals in that after a fast of 96 hours the blood sugar level of the dwarf is considerably lower than that of normal animals. It is generally agreed that the secretion of the adrenal cortical steroid hormones is largely controlled by anterior pituitary adrenocorticotrophin (ACTH). The dwarf, representing a hypopituitary state, is deficient in ACTH(12). It may be suggested, therefore, that the hypoplastic condition of the anterior pituitary and the adrenal cortex in the dwarf is associated with functional deficiencies of hormones which are normally concerned with the metabolism of carbohydrates. This imbalance in the adrenal-pituitary axis in the dwarf might best explain the severe hypoglycemia which develops under the stress of fasting.

However, in the light of the researches of Houssay and Anderson(15), and De Bodo *et al.*(16) relating the growth hormone to carbohydrate metabolism, it is not unlikely that the unique blood sugar pattern found in the fasting dwarf mouse may be partly explained by the animal's deficiency in growth hormone. Experiments designed to gain information on this problem are in progress.

Summary. Under the experimental conditions employed, findings may be summarized as follows: 1. Average blood sugar values for fed hereditary hypopituitary dwarfs are slightly, but not significantly, lower than those of fed normal mice. 2. The blood sugar level of fasting dwarfs drops precipitously to a minimum of 68 mg % after 96 hours. In contrast, normal mice exhibit a lesser drop, followed by some recovery which later gives way to a minimum average of 103 mg % after 96 hours of fasting. 3. These findings show that the sensitiveness of the dwarf to fasting is somewhat like that reported for hypophysectomized animals. This sensitivity herein reported, as judged by the severe hypoglycemia which develops under the stress of fasting, might best be attributed to the known imbalance in the adrenal-pituitary axis in the dwarf.

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