Hypoglycemia Produced by Purified Anterior Pituitary Growth Hormone and Its Relationship to the Pancreas.*† (18377)

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In previous publications(1-3) we demonstrated that purified anterior pituitary growth hormone exerts a potent anti-insulin action in hypophysectomized dogs. Within 18 hours of the first injection of growth hormone the exaggerated hypoglycemic response to insulin was diminished, and upon continued administration of the hormone the hypersensitivity to insulin was completely abolished. In addition, a concomitant diabetic state was produced.

Under certain circumstances, however, the administration of growth hormone was followed by a marked hypoglycemic response. A similar effect has been described by several investigators(4,5). This report is concerned with this hypoglycemia and its relationship to the pancreas.

Methods. This study was carried out on hypophysectomized dogs‖¶ and on acutely depancreatized, but otherwise intact, dogs. A part of the duodenum was resected in conjunction with the pancreatectomy, thereby assuring complete removal of the islet tissue and also minimizing liberation of insulin due to excess manipulation of the gland. The pancreatectomies and the succeeding 6 to 7 hour experiments were done under sodium pentobarbital‖ anesthesia. The majority of the dogs maintained a blood pressure of approximately 100 mm of Hg. In none of the dogs did the pressure fall below 50 mm of Hg. The hypophysectomized dogs used were all maximally sensitive to the hypoglycemic action of insulin(6-7). The insulin sensitivity tests were performed on trained unanesthetized dogs as described in an earlier publication(6); insulin (Lilly**) 0.025 unit/kg being used in all tests. Purified anterior pituitary growth hormone, Armour Lot No. 22KR1,†† was used in this study. Growth hormone of the same lot number was found to exert the anti-insulin action discussed above. In the experiments performed on the hypophysectomized dogs the dose of growth hormone varied from 0.3 to 1.0 mg/kg, administered intravenously. The dose of growth hormone used in the experiments on the acutely depancreatized dogs was 7.5 mg/kg, also given

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¶ Topical Thrombin, which was most helpful in controlling hemorrhage during the operation, was kindly supplied by Dr. A. C. Bratton, Jr., of Parke, Davis and Co.

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TABLE I. Effect of Growth Hormone (GH) and of Insulin (INS) on Blood Sugar of Hypophysectomized Dogs in the Post-Absorptive State.

(A) Time min.	Dog Hy8 Blood sugar in mg %			(B) Time min.	Dog Hy11 Blood sugar in mg %			
0	67	63	60	0	67	63	66	71
						GH†		
	INS* .025 μ/k	INS* .025 μ/k	GH† .5 mg/k		INS* .025 μ/k	1st day .6 mg/k	2nd day .6 mg/k	3rd day .6 mg/k
10	49	37	53	10	52	68	67	73
20	30	25	35	20	29	66	64	73
30	33	31	35	30	23	62	62	73
40	32	32	32	40	27	60	61	71
50	32	30	32	50	28	60	62	71
60	32	32	36	60	30	51	64	68
75	33	33	33	75	30	57	60	71
90	37	43	34	90		47	59	71
120	38	45	36	105	42			
150	37	53	34	120	48	38	54	63
180	42	55	35	150	48	40	57	71
210	48	63	34	180	54	38	57	70
240	56	63	34	210	57	43	62	66
				240	64	44	63	66
				420		70		

* Insulin intrav. at 0 time.
† Growth hormone intrav. at 0 time.

intravenously. Blood sugar determinations were done on venous blood samples, at frequent intervals, during the experiments.

Results. I. The results of representative experiments are recorded in Table I. When growth hormone was administered intravenously, for the first time, to 17 to 18 hours fasted hypophysectomized dogs a marked fall in blood sugar occurred. The onset and degree of this hypoglycemia may either be similar to that seen following the administration of insulin (Table I-A), or the onset may be delayed and the degree not as marked as after insulin (Table I-B). The duration of the hypoglycemia after growth hormone was longer than that seen after insulin in all the experiments. When a series of daily administrations of growth hormone were given (all intravenously and in the post-absorptive state), the hypoglycemic response appeared only after the initial injection (Table I-B). The progressively diminishing hypoglycemic response to the growth hormone injections was probably due, at least in part, to the development of the anti-insulin action brought on by growth hormone.

II. The growth hormone induced hypoglycemia has been attributed to an increased output of insulin, *i.e.* growth hormone exerts a pancreatotropic action. In an attempt to further elucidate the role of the islets of Langerhans in this hypoglycemia, the effect of growth hormone on the blood sugar of acutely pancreatectomized dogs was studied. Fig. 1 shows the blood sugar changes in 5 dogs following pancreatectomy. In 2 dogs the pre-operative blood sugar levels were higher than those generally observed. These 2 dogs were untrained and the high blood sugar values were probably due to increased adrenaline output. After removal of the pancreas the blood sugar steadily rose to hyperglycemic levels in each animal. Two of the dogs showed a slight and short lasting decrease in blood sugar 2½ and 3½ hours respectively after pancreatectomy. The blood sugar at the end of 6 to 7 hours varied between 152 and 509 mg %.

Several dogs were subjected to sham operations during which a portion of the jejunum was resected. No significant change in blood sugar occurred after the sham procedures. Thus, anesthesia, abdominal manipulation, and adrenaline secretion can be dismissed as factors responsible for the rise in blood sugar in the acutely depancreatized animals used in

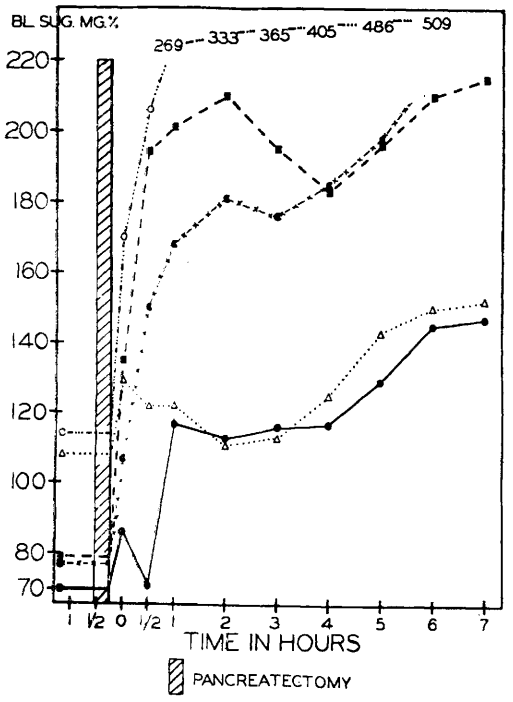

FIG. 1.
Blood sugar curves of 5 dogs during the 7 hours following pancreatectomy.

this study.

Fig. 2 shows the results following growth hormone administration to acutely pancreatectomized dogs. The pre-injection blood sugar levels were significantly above the pre-operative levels in 4 of the 6 dogs. Growth hormone was administered intravenously 38 to 48 minutes after removal of the pancreas. In every case a significant fall was apparent within 55 to 85 minutes of the injection of hormone. In 4 of the 6 dogs the blood sugar fell to levels as low as 35 to 54 mg % 3 to 5 hours after growth hormone. In the 2 instances in which the blood sugars were 158 and 202 mg % prior to the growth hormone injection, a significant decrease in blood sugar level occurred, but hypoglycemic levels were not reached. Toward the end of each experiment the blood sugar started to rise but in no case was the final blood sugar above the pre-growth hormone injection level; in fact in 5 of the 6 dogs it was below.

Discussion. It is evident from the data presented that purified anterior pituitary growth hormone is capable of producing a marked hypoglycemia in acutely depancreatized animals. The hypoglycemia observed in these animals must of necessity have been of extra-pancreatic origin. However, our experiments do not entirely exclude the possibility that in the intact animal the growth hormone induced hypoglycemia is due to some degree to a pancreatotropic action, *i.e.* a stimulation of insulin output from the islet cells.

Another aspect to be considered is that the acutely depancreatized animal is very probably not completely free of insulin. Therefore, the possibility exists that the presence of insulin is a necessary factor for the development of the growth hormone induced hypoglycemia.

Summary and conclusions. The administration of growth hormone to hypophysectomized dogs in the post-absorptive state results in a marked fall in blood sugar. This marked hypoglycemic response is seen only after the first of a series of injections of the hormone. The hypoglycemic effect of growth hormone also occurs in acutely depancreatized

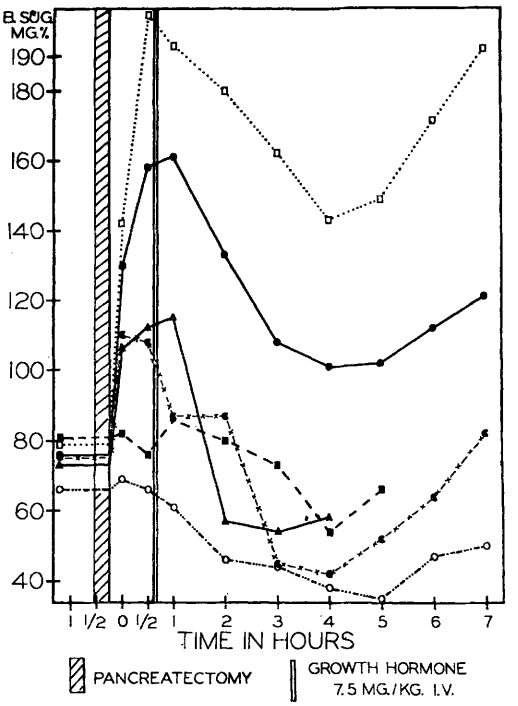

FIG. 2.
Effect of growth hormone on the blood sugar of 6 acutely depancreatized dogs.

dogs. It is concluded that the presence of the pancreas is not essential for the aforementioned action of growth hormone. However, it remains to be established whether insulin is a necessary factor for the growth hormone induced hypoglycemia.

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Effect of Pantothenic Acid Deficiency upon Adrenal Cortex, Thymus, Spleen, and Circulating Lymphocytes in Mice.* (18378)

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During the course of an investigation on the distribution of pantothenic acid in the tissues of adult male mice of the CF No. 1 strain, it was possible to make observations on the effect of a deficiency of this dietary requirement on the white blood cell count as well as structural changes in the adrenal cortex, spleen, and thymus(1). Such a study is desirable because of the established functional interrelationship between the secretory activity of the adrenal cortex, lymphoid tissue, and alterations in the circulating lymphocytes (2).

Lippincott and Morris made histopathological studies on young and adult C3H strain mice maintained on a diet deficient in pantothenic acid until death intervened in 6 to 8 weeks and reported a hyperkeratotic, atrophic, and desquamative dermatosis as well as myelin degeneration in the sciatic nerves and in the spinal cord. These investigators also stated that other organs, including the adrenals, were essentially normal in the deficient animals(3).

Experimental. Five mature mice, approximately 3 months of age, were fed a pantothenic-acid deficient ration No. 80 as described in detail by Morris and Lippincott(4). Four control animals of the same age received the same ration except that it was supplemented with d-calcium pantothenate at the rate of 30 mg per kg. All animals were weighed every 3 days throughout the experimental period of 7 weeks. Total white cell counts and blood smears, stained with Wright's stain, were made at weekly intervals. Tail-vein blood was used. For a histochemical study of the effect of pantothenic acid deficiency on the adrenal gland, thymus, and spleen, a second group of 22 mature male mice was used. Seven control animals were placed on pantothenate-containing ration and 15 on pantothenate-deficient ration. Individuals were killed at various intervals during an experimental period of 7 weeks to furnish tissues. In addition, 6 male mice were placed on a pantothenate-containing ration for 2 weeks, after which they were allowed to starve. The average duration of life of these animals was 6.3 days. One adrenal of each pair was prepared for frozen sections by fixation in 10% neutral formalin while the other was prepared for paraffin sections by fixation in Zenker-formol followed by postchromation in 3% potassium dichromate for 3 days. Thymus gland was also fixed for frozen and paraffin sections. Spleen was fixed in Zenker-formol for routine examination. Frozen sections were cut at 10 μ and paraffin sections at 6μ. Lipids were characterized in frozen sections by Sudan IV, Sudan Black B, Oil Red O, Schiff's reagent, and 2-4 dinitrophenylhydrazine(5). Heidenhain's iron alum

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