Loss of Insulin Hypersensitivity and Development of Diabetes in Hypophysectomized Dogs Produced by Purified Growth Hormone.*† (17960)

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It is well established that removal of the anterior pituitary gland renders the animal highly sensitive to the hypoglycemic action of insulin. Previous work from this laboratory(1) has shown that the hypersensitivity develops gradually following removal of the hypophysis, reaching its maximum in 5 to 6 weeks. Since the adrenal and thyroid glands undergo gradual atrophy when deprived of their hypophyseal tropic hormonal regulation, the role of these endocrine organs in insulin hypersensitivity was studied. Both thyroxin (2) and adrenal cortical extract(3) were found to antagonize the action of insulin. When very large amounts of a potent adrenal cortical extract were administered a marked anti-insulin action was noted. Nevertheless, it could not abolish the hypersensitivity. The present report deals with the effect of purified anterior pituitary growth hormone on the insulin response and the glucose tolerance of hypophysectomized dogs.

Method. This study was carried out on trained, unanesthetized normal and hypophysectomized dogs.§ Only those hypophysectomized animals were used that exhibited maximal insulin hypersensitivity. All insulin and glucose tolerance tests were started 17 to 18 hours after the last feeding. Unless otherwise stated, 0.025 unit of insulin (Lilly)‖ per kg body weight (the test dose) was given intravenously and the blood sugar changes followed for a 4 hour period. The response to intravenous glucose, 0.075 g/kg/min. for 10 min., was also followed for 4 hours. The growth hormone used was prepared by Armour and Co. (Lot No. 22KR1)¶ In the experiments to be reported the first dose of the hormone was always given intramuscularly in the afternoon and followed immediately by feeding. The second dose was given intravenously in the fasting state, 17 to 18 hours later. Thereafter, the hormone was administered intramuscularly. The daily dose of growth hormone was always 1 mg/kg body weight.

Results. A total of 68 insulin experiments were performed on normal and hypophysectomized dogs before and during growth hormone administration. In Table I we have recorded the results of representative experiments. The administration of the test dose of insulin to normal dogs produced no change in blood sugar or only a slight hypoglycemia of short duration. The response of normal dogs as recorded in Table I is a composite of the values obtained in 18 animals. The test dose of insulin in the hypophysectomized dog Hy9, as in all our hypophysectomized animals, produced a very marked hypoglycemia. Normal animals require 60 to 100 times the test dose to manifest a comparable hypoglycemic response(1). Two doses of growth hormone markedly diminished the hypoglycemic response to insulin in all the hypophysectomized dogs. After four or more doses the exag-

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1. Slater, I. H., De Bodo, R. C., Weisberg, H. F., and Kiang, S. P., *Fed. Proc.*, 1948, v7, 116.

2. Unpublished observations.

3. de Bodo, R. C., Kiang, S. P., and Slater, I. H., *Fed. Proc.*, 1949, v8, 32.

§ We would like to thank Dr. A. C. Bratton, Jr., of Parke, Davis and Co. for supplying the Topical Thrombin which was most helpful in controlling hemorrhage during the operation.

‖ Insulin was kindly supplied by Dr. K. K. Chen of Eli Lilly and Co.

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TABLE I.
Insulin Sensitivity and Glucose Tolerance Tests in Normal and in Hypophysectomized Dogs Before and During Growth Hormone (GH) Treatment.

	(A) Insulin sensitivity tests					(B) Glucose tolerance tests			
	Normal	Hy9				Normal	Hy9		
		Doses of GH*					Doses of GH*		
	0	0	2	9		0	0	14	
Time in min.	Blood sugar in mg %				Time in min.	Blood sugar in mg %			
0	77	63	73	102	0	79	61	110	
	Insulin .025 u/kg intrav. at 0 time					Glucose .075 g/kg/min. intrav. for 10 min.			
10	67	49	64	100	10	261	272	332	
20	66	35	55	96	15	205		314	
30	74	24	54	94	40	104	127	264	
40	75	29	54	92	50		86		
50	77	31	53	92	55	85		256	
60	77	29	49	92	60		54		
75		32	54	95	70	82		246	
90		35	53	92	85	83	57	236	
120		34	55	103	100	80	52	220	
150		38	59	108	115	80		204	
180		39	60	103	145	80		174	
210		40	60	104	160	79	50	162	
240		40	59	103	190		†	146	
					220		†	130	
					250		†	117	

* Dose of growth hormone: 1 mg/kg body wt.
† Convulsions.

gerated response to insulin disappeared. In fact, after prolonged administration of growth hormone the hypoglycemic response in the hypophysectomized animal following 1.5 units of insulin per kg was less than that in normal animals.

Representative results of 28 intravenous glucose tolerance tests in normal and hypophysectomized dogs before and during growth hormone administration are also recorded in Table I. The untreated hypophysectomized dog responds to intravenous glucose like the normal animal, except for a characteristic secondary hypoglycemic phase. The growth hormone treated hypophysectomized dogs displayed the type of response to intravenous glucose infusion which occurs in diabetic animals, *i.e.*, the blood sugar rose to higher levels and the return to the fasting level was very much delayed. It is noteworthy that the secondary hypoglycemic phase disappeared. An impaired glucose tolerance was observed as early as after 2 doses of growth hormone. Continued administration of the hormone resulted in progressive impairment of the glucose tolerance. A further indication of the diabetogenic action of purified growth hormone was the progressive elevation of the fasting blood sugar noted after daily hormone administration (Table I). The elevation of the fasting blood sugar level is more apparent when compared to the low fasting blood sugar level of untreated hypophysectomized dogs. We did not note either glycosuria or acetonuria in hypophysectomized animals during the growth hormone treatment.

While this work was in progress Young and his colleagues(4) reported the production of glycosuria in normal cats with purified growth hormone. Quite recently Houssay and Anderson(5) obtained diabetes in partially depancreatized dogs and cats treated with large doses of growth hormone.

Discussion. It is evident from our experiments that the marked insulin hypersensitivity of the hypophysectomized dogs was completely abolished by the administration

4. Cotes, P. M., Reid, E., and Young, F. G., *Nature,* 1949, v164, 209.

5. Houssay, B. A., and Anderson, E., *Endocrinology,* 1949, v45, 627.

of purified growth hormone. When this occurred an impairment of glucose tolerance, *i.e.*, a diabetic state, was also present. Evans and his colleagues(6) have shown that growth hormone produces nitrogen retention and lowers the blood amino nitrogen. In our experiments, therefore, increased gluconeogenesis, as a factor accounting for the loss of hypersensitivity and the diabetic state, can be minimized. The alteration in carbohydrate metabolism effected by growth hormone must be attributed to decreased carbohydrate utilization. That peripheral utilization of carbohydrate is diminished by purified growth hormone, is supported by the work of Stadie *et al.*(7) and Park *et al.*(8). These investigators found a decrease in carbohydrate utilization in the isolated diaphragm of growth hormone treated rats. It is apparent from our work that a physiological antagonism exists between growth hormone and insulin. In view of this latter phenomenon, the effects of growth hormone administration to intact animals are in all likelihood greatly modified by compensatory adjustment of the insulin-secreting cells of the pancreas. If the islets of Langerhans of growth hormone treated animals had been able to adequately adjust themselves to the peripheral inhibition of carbohydrate utilization by increasing their insulin output, no impairment of glucose tolerance would have been observed.

It is our opinion that in the hypophysectomized animal the absence of endogenous growth hormone is an important factor in causing the insulin hypersensitivity. If we had succeeded in obtaining physiological levels by hormonal replacement therapy, we certainly should not have observed a diabetic state. We consider the impairment of glucose tolerance induced by growth hormone to be the result of overdosage, an exaggerated manifestation of a physiological process.

Summary. The insulin hypersensitivity characteristic of hypophysectomized dogs was completely abolished by purified anterior pituitary growth hormone. Concomitantly an impairment of glucose tolerance, *i.e.*, a diabetic state, was produced.

6. For references see Li, C. H., and Evans, A. M., Recent Progress in Hormone Research, Academic Press, Inc., New York, 1948, v23, pp. 3-44.

7. Stadie, W. C., Haugaard, N., Hills, A. G., and Marsh, J. B., *Am. J. M. Sc.*, 1949, v218, 275.

8. Park, C. R., and Krahl, M. E., *J. Biol. Chem.*, 1949, v181, 247

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Effects of B-Diethylaminoethyl Xanthene 9-Carboxylate Methobromide (Banthine*) on Human Gastrointestinal Function.† (17961)

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Medical therapy in peptic ulcer has relied to a considerable extent upon agents that will neutralize or buffer the acid gastric juice which appears to be so important in the production of peptic ulcer. In searching for medication to prevent or diminish the production of acid gastric secretion, the belladonna derivatives, notably atropine, have been used because of their effect as para-sympathetic antagonists. The usefulness of this group of drugs has been limited because depression of gastric secretion is not affected unless other physiological side effects are produced(1,3). There are also unpredictable individual tol-

* Banthine furnished by courtesy of G. D. Searle Co., Chicago, Ill.

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