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Hyperglycemia in Response to Hypoglycemia in Normal and Hypophysectomized Dogs.

MICHAEL SOMOGYI, T. E. WEICHSELBAUM AND PETER HEINBECKER.

From the Laboratories of the Jewish Hospital and the Department of Surgery, Washington University School of Medicine, St. Louis, Mo.

Somogyi[1] has observed on diabetic as well as on non-diabetic human beings that hypoglycemia is followed by a compensatory hyperglycemia. After hypoglycemia in the postabsorptive state the blood sugar rises and in many cases temporarily exceeds the fasting level. In other words, there is a hyperglycemia relative to the fasting blood sugar. This phenomenon has not been generally noted because most workers do not observe the course of the blood sugar level long enough following hypoglycemia.

We report here the occurrence of the same phenomenon in normal and in hypophysectomized dogs, observed during studies of their

TABLE I.
Hyperglycemia Following Hypoglycemia in Dogs.
Figures represent mg. of glucose per 100 cc. blood.

Dog No.	Date	Time in Min. after administration glucose 0	30	60	90	120	180	240	300	360	Mg. % Increase
Normals											
105*	4/24/36	*81*	111	108	89	82	83	81	*87*		6
107*	2/11	*84*	116	99	82	*92*	84	80			8
108*	4/6	*75*	95	85	79	65	*81*	78			6
110*	3/30	*88*	103	98	88	*93*	92	94			5
A.1*	4/6	*87*	128	144	106	79	90	*94*			7
B.48†	7/16	*79*	66	*84*	83						5
06†	10/2	*77*	—	94	88	86	*107*	97	92	92	30
A.6†	7/16	*77*	121	64	—	*81*	76	78	79	75	4
B.38†	2/1/37	*76*	159	58	83	*87*	85	83	82	82	10
016†	2/16	*69*	114	72	73	71	*80*	73	74	73	11
08†	2/16	*76*	225	120	76	72	76	78	78	*81*	5
Hypophysectomized											
112*	12/31/35	*81*	114	124	101	77	86	*92*			11
A.1*	7/7/36	*79*	104	89	64	64	81	*85*	85		6
B.51*	7/7	*69*	84	83	73	68	71	*74*	69		5
06†	11/16	*60*	154	63	*76*	70	67	67	66	68	13
A.6†	11/16	*55*	114	55	56	60	61	63	63	*65*	10
B.1†	11/12	*53*	118	58	43	44	*63*	63	61	61	10
B.38†	4/5/37	*72*	366	256	151	101	66	64	73	*83*	11
016†	4/5	*66*	251	79	59	68	77	75	72	*77*	11
08†	3/15	*72*	199	49	55	77	73	77	74	*81*	9

*0.85 gm. of glucose per kg. body weight *per os.*
†1.50 gm. of glucose per kg. body weight intravenously.

[1] Somogyi, M., unpublished.

carbohydrate metabolism. Hypoglycemia was produced by 2 different procedures: (1) by oral or intravenous administration of glucose; (2) by intravenous injection of moderate doses of insulin.

In the first type of experiment, several hours after the administration of glucose the blood sugar fell below the fasting level, and this hypoglycemia was followed by hyperglycemia within 6 hours after the administration. It may be seen in Table I that the compensatory hyperglycemic response after hypoglycemia occurred in hypophysectomized animals about as in the normals.

In the second group of experiments, hypoglycemia that did not reach the convulsive level was the result of the injection of insulin in moderate doses. As shown in Table II, the compensatory hyperglycemic response again appeared, as after the hypoglycemia elicited by the administration of glucose, both in normal and in hypophysectomized dogs.

TABLE II.
Hyperglycemia Following Hypoglycemia in Dogs.
Figures represent mg. of glucose per 100 cc. blood.

		Time in Min. after administration insulin									Mg. %
Dog No.	Date	0	30	60	90	120	180	240	300	360	Increase
Normals											
319*	6/17/36	*88*	64	62		93	*95*	93	92	95	7
A.4†	3/20	*79*	60	52		58	73	88	90	*93*	14
A.5†	2/21	*64*	50	56		64	75	80	*82*	82	18
B.51*	6/17	*68*	49	55		*72*	57	59	63	68	4
B.35*	6/17	*64*	67	60		60	70	*73*	70	73	9
06†	10/5	*68*	40	44		65	77	*82*	77	81	14
A.6†	10/5	*72*	43	39		58	71	73	74	*75*	3
B.75†	10/12	*88*	52	69		95	99	*101*	99	99	13
B.1†	10/12	*71*	40	35		50	67	*76*	75	73	5
105†	5/7	*66*	48	42		60	*89*	89			23
B.45†	10/5	*66*	42	35		65	*79*	77	76	79	13
05†	10/12	*80*	49	43		56	74	78	*91*	84	11
A.1†	4/7	*82*	68	49		59	73	*91*			9
B.38‡	1/29/37	*77*	64	43	52	63	83	82	*84*	84	7
016‡	1/29	*69*	67	31	37	46	63	82	*86*	84	17
08‡	1/29	*78*	47	54	66	83	83	*89*	80	82	9
Hypophysectomized											
A.4*	6/1/36	*74*	31	38		52	74	85	*88*	85	14
A.5*	6/25	*60*	43	49		61	73	68	*76*	76	16
B.35*	7/6	*63*	41	40		51	68	75	74	*78*	15
06*	11/12	*65*	45	32		48	58	71	*74*	74	9
A.6*	11/12	*65*	35	37		59	70	*76*	71	71	11
B.37*	6/1	*72*	38	31		36	58	82	82	*88*	15
B.38§	3/8/37	*52*	45	24	27	34	50	57	56	*61*	9
016§	3/8	*70*	29	22	33	37	63	69	*80*	79	10
08§	3/30	*71*	32	25	28	37	53	72	*83*	77	12

Dosages: * = 0.25 U/kg. body wt. all intravenous.
† = 0.5 U/kg.
‡ = 0.3 U/kg.
§ = 0.15 U/kg.

Instances of hyperglycemia in response to hypoglycemia are to be found in blood sugar curves after the injection of insulin, in experiments reported by Lucke, Heydeman and Hechler,[2] MacLeod,[3] and Scott and Dotti.[4] Scott and Dotti are the only ones to comment on it. With small doses of insulin, they state, "there may be a late hyperglycemia, occurring when the returning curve overshoots the original sugar level. This reminds one of the hypoglycemia so commonly seen in dextrose tolerance curves, though, of course, it is the reverse phenomenon."

Their remark is very much to the point. Whenever the glycemic level is changed from the normal fasting level, a compensatory change in the regulatory mechanism ensues to restore the original level. The remarkable constancy of the postabsorptive (fasting) level of glycemia is the result of a finely regulated balance between the glycogenolytic and glycogenetic processes.

When the blood sugar is raised to hyperglycemic levels, the compensatory hypoglycemia is usually attributed to the discharge of extra insulin as the result of a stimulus exerted by the hyperglycemia. The work of Soskin and Allweiss[5] seems to indicate that the hypoglycemic response may set in without extra insulin, as if hyperglycemia in itself could either depress glycogenolysis or intensify glycogenesis. This, of course, does not mean that insulin under physiological conditions has no part in the process; it is likely, however, that insulin is but one of the factors responsible for it. For the time being, it can only be said that upon the appearance of hyperglycemia a shift takes place in the balance between glycogenolytic and glycogenetic factors, causing the glycogenetic factors to outstrip the glycogenolytic ones. It is impossible at present to say whether this is the result of an increased activity of the former, or of a diminished activity of the latter, or whether both changes take place at the same time. The fact remains, however, that when a compensatory shift occurs in the relationship of the 2 factors, in many cases an overcompensation ensues, so that after hyperglycemia variable degrees of hypoglycemia are produced.

In contrast to hyperglycemia, hypoglycemia effects a shift in the balance between glycogenolytic and glycogenetic factors in such a manner as to cause the glycogenolytic activity to outstrip the glyco-

2 Lucke, H., Heydeman, E. R., and Hechler, R., *Z. f. d. ges. exp. Med.*, 1933, **87**, 103; **88**, 65.

3 MacLeod, J. J. R., *Carbohydrate Metabolism and Insulin*, 1926, Longmans, Green and Company, Ltd., London.

4 Scott, E. L., and Dotti, L. B., *Arch. Int. Med.*, 1932, **50**, 511.

5 Soskin, S., and Allweiss, M. O., *Am. J. Physiol.*, 1934, **110**, 4.

genetic. Here again the compensatory process frequently overshoots and produces a hyperglycemia in the sense that the blood sugar rises temporarily above the fasting level. This does not happen in all animals. In our experiments, the hypoglycemia which occurs following the administration of glucose elicited hyperglycemia in 11 out of 27 normal, and in 9 out of 21 hypophysectomized dogs. Insulin-hypoglycemia was followed by hyperglycemia in 16 out of 24 normal, and in 9 out of 21 hypophysectomized animals. The extent of the hyperglycemia shows considerable individual variations; in a few cases it represents a rise of no more than about 5 mg. % above the fasting level.

The question may be raised as to whether such apparently trivial differences are sufficiently beyond the limits of analytical errors as to deserve consideration. The analytical technique employed in this work warrants an answer in the affirmative. True sugar values were determined by the copper-iodometric method with the Shaffer-Somogyi reagent No. 50[6] in filtrates prepared by Somogyi's copper precipitation method.[7] This procedure, in the hands of various workers in this laboratory, yields duplicate values which, as a rule, check within 1 mg. %; the maximum discrepancy between duplicate determinations is 2 mg. %.

Thus if blood sugar values showed differences of more than 1 to 2 mg. %, these were safely beyond the limits of experimental errors and represented actual changes in the blood sugar level.

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Development of Autonomic Innervation Correlated with Reactivity of the Fetal Pig Iris.

KERMIT CHRISTENSEN.

From the Department of Microanatomy, St. Louis University School of Medicine.

The results of recent studies of the responses of developing organs to certain choline esters have suggested an important rôle of the nerves in the initiation and progressive development of these reactions. Armstrong[1] has shown that when the embryonic Fundulus heart is differentiated to the adult morphology but is, as yet, without

6 Shaffer, P. A., and Somogyi, M., *J. Biol. Chem.*, 1933, **100**, 695.

7 Somogyi, M., *J. Biol. Chem.*, 1931, **90**, 725.

1 Armstrong, P. B., *J. Physiol.*, 1935, **84**, 20.