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Glucose Tolerance in Decerebrated Rats After Relatively Long Survival.

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It has been amply demonstrated in acute experiments on rabbits and cats that piqûre or decerebration at the pontile level gives rise within less than an hour to hyperglycemia and glycosuria, and that the increase in sugar is usually maintained for 3 or 4 hours, but may last as long as 9 hours. Claude Bernard[1,2] observed that piqûre was most effective when done bilaterally at levels between tthe emergence of the vagus and acoustic nerves. Donhoffer and Macleod[3] demonstrated that hyperglycemia occurred consistently only when decerebration was done at the pontile level, and they were of the opinion that the diabetogenic center probably was situated in the tegmentum pontis. Brooks[4] presented evidence that the center is situated in the floor of the IVth ventricle just caudal to the middle of the brachium pontis and very close to the vasomotor center.

According to Donhoffer and Macleod,[3] midbrain decerebration leads to little or no hyperglycemia, an observation in accord with those of Olmsted and Logan,[5] Bazett, Tychowski and Crowell,[6] Peterson,[7] and Noltie.[8] On the other hand, a high and well sustained hyperglycemic response to midbrain decerebration has been noted by Anderson *et al.*[9] and Evans, Tsai and Young.[10]

The medulla oblongata also has been subjected to piqûre or other lesion in an effort to locate a diabetogenic center. Brugsch, Dresel and Lewey[11] came to the conclusion that the dorsal nucleus of the vagus was the center in point. On the other hand, Hiller[12] and Hiller and Tannenbaum[13] found relatively little increase in blood sugar following damage to this nucleus, and they contended that no blood-sugar-raising (or diabetogenic) center, as such, exists in the central nervous system, but their view depends on what definition the term "center" is given. According to Donhoffer and Macleod[3] and Macleod,[14] only a slight or moderate degree of hyperglycemia ensues after injury to the medulla oblongata.

The rat has been little used in experiments on decerebration-induced or piqûre-induced hyperglycemia. Bell, Horne and Magee[15]

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TABLE I.
Blood Sugar Values Within Four Hours After Pontile Decerebration.*

Rat No.	Blood sugar (mg %)			
	Preoperative (under anesthesia)	Postoperative		
		Immediate	1 hr	4 hr
Decerebrated rats				
651	—	—	209	140
650	74	51	208	219
654	84	68	64	123
655	80	155	118	196
656	87	142	218	99
Control: partially decorticated rats				
507	—	—	86	84
300	59	86	86	78
301	77	156	95	58
302	70	155	87	72

* The extent of the lesions was verified on gross examination post mortem.

found that pontile decerebration caused no increase in blood sugar in fasted rats or in those on a well balanced diet, but did occur over a 2-hour period if they had been fed a diet rich in carbohydrates. They were unable to elicit hyperglycemia by midbrain decerebration.

All the decerebration experiments referred to were acute ones, the animals generally surviving not more than a day or two. It is the purpose of this communication to describe the effects of decerebration on the glucose tolerance of rats which survived the operation for from 4 to 20 days.

Methods. Young adult female rats of the Sprague-Dawley strain were used in this study. All had had access to food up to the time of operation. Sodium pentobarbital, 2.5 mg per 100 g body weight intraperitoneally, was the general anesthetic employed. Novocaine (2.0% solution) was used to infiltrate the scalp immediately before opening the skull. Just preceding the operation, 0.05 cc of calcium gluconate per 100 g body weight was given intravenously to facilitate clotting. Decerebration was done at pontile and midbrain levels. Using the dorsal approach, wedges of brain tissue were removed by suction, and an incision then made downward to the base of the skull.

There were two objectives in this study: a) to determine the blood sugar level within a short time after decerebration, and b) to study glucose tolerance after the lapse of several days.

a. In one series of rats, blood sugar levels were determined at the following intervals: 1) preoperatively, just after the animals had been anesthetized, 2) immediately following operation, 3) one hour after operation, and 4) 4 hours after operation.

b. In the other series the animals were given 10 cc of 10% glucose in saline parenterally 6 hours after decerebration. Twenty-four hours postoperatively they were placed on a regimen consisting of 10 cc liquid diet by stomach tube twice daily and 10 cc of 10% glucose in saline and 2500 units penicillin parenterally once a day. From the start they were kept in an incubator at a temperature of 27°C, and under these conditions their rectal temperature was usually 33 to 34°C. Serving as controls were 3 rats, one of which was partially decorticated, one hemidecerebrated, and one normal. These were kept on the same regimen as the experimental animals.

The glucose tolerance test was done on the animals at various times from the 3d to the 23d day after operation. For 17 hours before the test the animals were fasted; they also received no water until one hour before the test, when they were given 10 cc of physiologic solution of sodium chloride by the subcutaneous route. Just before the test was begun, the animals were lightly anesthetized by sodium pentobarbital 2.5 mg per 100 g

TABLE II.
Data on Glucose Tolerance and Autopsy Findings in Decerebrated Female Rats and Controls.

Rat No.	Wt (g)	Operation	Postoperative data: Day	Wt (g)	Glucose tolerance (blood sugar in mg %): Fast.	30 min.	60 min.	90 min.	120 min.	Survival (days)	Died (D) or sacrificed (S)	Autopsy data: Wt (g)	Autopsy data
							Experimental						
343	174	Pontile Decerebration	4	158	120	—	278	398	456	18	D	157	Virtually complete destruction of pons to lower level of trapezoid body.
323	192	Pontile Decerebration	3	205	141	336	442	464	480	4	D	203	Decerebration at midpontile level grossly; microscopic examination not done.
312	187	Pontile Decerebration	7	172	108	117	380	440	504	14	S	169	Virtually complete destruction to lower level of pons.
336	140	Pontile Decerebration	3 6	138 141	84 97	285 247	271 300	— 305	... 326	9	D	126	Complete destruction of pons to level of 7th nerve.
309	216	Midbrain Decerebration	5	196	85	304	420	170	140	20	S	171	Softening of tissue of rostral midbrain equivalent to midbrain decerebration.
							Control						
351	153	Partial Decortication	1 23	143 136	85 >35	111 105	141 140	— 136	— 136	23	S	136	Brain stem intact except superficial softening of dorsal thalamus bilaterally and dorsal epithalamus at one level.
304	169	Pontile hemidecerebration	7 13	134 128	101 79	222 162	204 88	224 80	242 85	13	S	128	Lateral 1/3 to 3/4 of brain stem destroyed unilaterally to lower level of trapezoid body.
318	175	None	5	170	67	193	243	248	229	18	S	165	No histologic changes observed.
43 normal rats (avg)			—	182	76	154	182	179	183	—	—	—	—

body weight. They were then placed in an animal holder with the tail resting on a warm plate. Blood was collected from the tip of the tail. After the fasting blood sample was taken, 5 cc of 20% glucose solution per 100 g body weight were given by stomach tube. Blood samples were taken every 15 minutes for 2 hours. During the glucose tolerance test the animals were quiet, and the rectal temperatures of the decerebrated animals were between 33° and 35°C. Over the period of several weeks during which these tests were carried out, glucose tolerance was done also on 43 normal female rats of the same age. For blood sugar determinations the micro-method of Haslewood and Strookman[16] was used.

At autopsy the brains were fixed in 10% formalin. Blocks were frozen and serially sectioned at 45 microns by the method described by Marshall,[17] and an average of 50 sections per case were stained, one-half by cresyl violet and the other half by a modified Weil myelin sheath method.

Results. a. Blood sugar values within 4 hours after pontile decerebration are indicated in Table I. In neither the decerebrated nor the partially decorticated animals was there an elevation of blood sugar following anesthetization. Immediately after operation, which required about 30 minutes, the blood sugar was somewhat elevated in about half the experimental and control groups. Subsequently there was hyperglycemia in the experimental animals, but not in the controls.

b. Glucose tolerance in rats of longer survival is shown in Table II. The studies were made on these animals from the 3d to the 7th day after operation. The decerebrated rats showed a fasting blood sugar which tended to be normal, but had a decreased tolerance for fed glucose, the blood sugar rising to levels between 450 to 500 mg % at the end of the second hour, except in one animal (rat 336) in which it was 326 mg %. The fifth rat in this series was subjected to decerebration at the midbrain level; it also showed a diminished tolerance for fed glucose, but the highest peak in the blood sugar curve appeared after one hour, and by the second hour the blood sugar level approached normal. The partially decorticated and hemidecerebrated control rats showed glucose tolerance curves which were in the normal range when comparison is made (1) with the values in an unoperated animal (rat 318) subjected to the same regimen as the experimental animals, and (2) with the average values of 43 normal rats which had been fed *ad libitum.*

In order to rule out extraneous factors affecting blood sugar, such as the handling of the decerebrated animal during the glucose tolerance test, a sham test was carried out; it differed from the regular test only in that water rather than glucose solution was given by stomach tube. That the factor of handling was of no import is indicated by the observation that blood sugar values prior to the giving of the water and every 15 minutes thereafter for 2 hours were found to range between 94 and 119 mg%.

Discussion. The experiments herein described differ from those previously reported in that the blood sugar studies were done on the 3d to the 7th day after decerebration. The tests were performed while the animals were in a "healthy state," as indicated by the length of the subsequent survival periods, which in one case was as long as 20 days. It will be necessary to repeat the work on decerebrate animals of longer survival before the duration of the disturbance in carbohydrate metabolism can be determined.

Another aspect of the work was the determination of blood sugar values during the few hours after decerebration. Hyperglycemia of moderate degree over about 4 hours occurred consistently in animals which had had access to food up to the time of operation. This observation differs from that of Bell, Horne and Magee, previously referred to, who found that hyperglycemia occurred only in animals fed a rich carbohydrate diet: ours had been on a standard stock diet. Thus, it would appear that the rat is no different from the rabbit and cat so far as the induction of

[16] Haslewood, G. A. D., and Strookman, T. A., *Biochem. J.*, 1939, **33**, 920.

[17] Marshall, W. H., *Stain Technol.*, 1940, **15**, 133.

hyperglycemia by decerebration is concerned.

This study confirms the well authenticated observation that disordered carbohydrate metabolism is most striking when decerebration is done at the pontile level. Unilateral piqûre of the floor of the IVth ventricle has been reported by several workers, including Claude Bernard, to give rise to transient hyperglycemia, but in one of our control animals (rat 304), in which the pons and midbrain were destroyed unilaterally up to the midline, the glucose tolerance was normal.

Under autopsy data in Table II, only the lower levels of the lesions are indicated, for these are regarded as the significant ones. At operation, considerable brain tissue was removed in order to be sure that decerebration was complete. In each of the animals decerebrated at the pontile level, autopsy studies disclosed either softening or absence of the midbrain, the epithalamus, the superior cerebrum, the hippocampus, and part or all of the thalamus, bilaterally. Free from lesions were the pituitary gland, hypothalamus, subthalamus, and lenticular nuclei, though in one instance (rat 343) the superior part of the hypothalamus at the infundibular level was softened. In the animal listed as having been subjected to midbrain decerebration (rat 309), the original intent was to do a decortication and have the animal serve as a control, but microscopic examination of serial sections of the brain disclosed destruction of the posterior thalamus, the most superior part of the hypothalamus, the pretectal region, the inferior colliculi, and the medial geniculate bodies, with softening of the lateral two-thirds of the rostral midbrain bilaterally.

Summary. Rats decerebrated at the pontile level exhibited a markedly elevated glucose tolerance curve 3 to 7 days after operation. One subjected to midbrain decerebration showed a shallower and less sustained curve. Hyperglycemia occurred in rats during the first few hours after pontile decerebration, which is in confirmation of previously published results on rabbits and cats.

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Effect of an Analogue of DDT on Experimental Murine Typhus.

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In a search for rickettsiostatic agents that might be more effective than para aminobenzoic acid (PABA), a large group of miscellaneous substances has been tested in mice infected with murine typhus. The results obtained with one of these, 1,1,1-trichloro-2, 2-bis(para-nitrophenyl) ethane, a nitro analogue of DDT, seem to warrant a brief report at this time.* This compound, which will hereafter be referred to as the nitro analogue, was being tested in mice by Kikuth in Germany at the time of the surrender. Nothing is known of his experiments except his notation that the compound was more effective against murine typhus than was methylene blue, and that it was of low toxicity.[1]

We have been successful in treating mice infected with murine typhus with material prepared in this laboratory.† Mice of the

* This substance was named Nitrogesarol by the Germans, a term which would erroneously lead to the belief that it was obtained as the result of the nitration of DDT.

1 Publication Board Reports, Dept. of Commerce, Report No. 248, p. 63.

† We are indebted to Dr. E. J. Cragoe, Jr., of the Organic Chemistry Department for the preparation of this compound.