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Influence of Vagi and Splanchnics upon Blood Sugar Response to Glucose Administration.*

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(Introduced by David Rapport.)
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The rôle of the parasympathetic and sympathetic nervous systems in the regulation of the blood sugar level has been studied by a number of investigators. A review of the literature impresses one first with the vast amount of work done, second with the diversified and, in many instances, ingenious methods of approach to the problem, and third with the lack of uniformity of the results obtained by the various observers.

The earlier work centered chiefly about the influence of the parasympathetic nerves over the regulation of the blood sugar level. The results in some cases pointed to the presence in the vagus nerves of secretory fibers to the pancreas, in others to the presence of tonic inhibitory fibers, and in still others to the presence of neither secretory nor inhibitory fibers. Among the methods of experimentation have been stimulation of isolated portions of the vagi and section of the same at different levels. Of the experiments in which the nerves had been cut, the majority have been performed after section either in the neck or thorax. Clark,[1] working on cats, severed the vagus nerves below the diaphragm and found increased tolerance to glucose. So far as we are aware there has been no similar work done in dogs after section of the vagus nerves at this level.

Attention has also been called to the rôle played by the sympathetic system. The methods employed here have consisted variously of lumbo-abdominal sympathectomies, splanchnic nerve sections at different levels, cœliac ganglionectomies, and adrenal denervations. The effect of such procedures on tolerance to glucose and on experimentally produced diabetes has been studied and the results obtained have been just as contradictory among themselves as have been those in the case of the parasympathetic system. We have omitted reference to the large literature due to consideration of space.

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[1] Clark, G. A., *J. Physiol.*, 1931, **73**, 297.

Recently de Takats and his collaborators, having obtained what they regarded as significant increases in glucose tolerance in dogs after cœliac ganglionectomy, adrenal denervation, and splanchnic nerve section, have used their results as a basis for justifying splanchnic nerve section in human cases of diabetes. The results on 3 cases have been reported.[2] Of these, one was classified as a partial failure mainly due to incomplete operation, and another as a complete failure due to improper selection of the patient. The third case has since operation required a smaller daily dosage of insulin.

We here report the effects on glucose tolerance of the following procedures: (1) subdiaphragmatic vagus section; (2) cœliac ganglionectomy following double vagus section; (3) removal of the left adrenal and denervation of the right; (4) cœliac ganglionectomy following removal of one adrenal and denervation of the other.

The observations were made on 5 adult female dogs, weighing between 6-11 kilos each, and living on a constant maintenance diet which included cracker meal, lard, lean beef heart, bone ash, cod liver oil, and dried yeast. A fasting period of 41 hours was allowed, at the end of which time the animal was catheterized and a fasting blood sample of approximately 8 cc. withdrawn from the external jugular vein. A solution of freshly prepared 50% glucose was then injected intravenously, the amount being 1 cc. per kilo of body weight. Samples of blood were drawn at 10, 20, 40, 60, 90, 120, and in some cases 180 minutes after the time of injection. Following the withdrawal of the last blood sample, the animal was again catheterized and the urine obtained added to any that may have been voided during the course of the experiment. The blood samples were analyzed for sugar by the modified Folin-Wu method. Urinary sugar was determined by the micro Benedict method. This standardized procedure was carried out in each series of experiments performed before and after the operations.

The operative procedures were carried out with aseptic precautions and under ether anesthesia. They consisted variously of section of the vagus nerves, subdiaphragmatically, removal of one adrenal and denervation of the other, and cœliac ganglionectomy. In order to allow for recovery after operation, no observations were made until after 7-10 days, at which time healing of the wound had occurred. In each case, final observations were made several months after operation.

[2] de Takats, G., *Ann. Surg.*, 1935, **102**, 22.

Effect of vagus section. The effect of vagotomy on the blood sugar level curve after administration of glucose was studied in 4 dogs. In dog No. 1, after vagus section on the left side only, and in dog No. 2 after section on the right side only, there was no change in the tolerance to glucose as compared with the established normal. Following left vagus section in dog No. 2, the glucose tolerance curves showed a slight departure from the controls at points taken 40 and 60 minutes after injection. The blood sugar values obtained here were 25-30 mg. per 100 cc. of blood higher than in the controls. However, the values after 60 minutes and up to 180 minutes were in harmony with the controls for the same time interval. We do not consider the variations significant. After simultaneous bilateral vagotomy in dogs 3 and 4, the tolerance to glucose remained unchanged. In none of the observations after vagus section did the total output of urinary sugar for the period of experimentation materially change after operation.

The results found in dogs 1, 2, and 3 are shown in Tables I, II, and III.

TABLE I.
Dog No. 1.
Blood Sugar in mg. per 100 cc.

	Controls				After Left Vagus Section			
Time (min.)	Exp. 1 Wt.–9.0	Exp. 2 Wt.–9.2	Exp. 3 Wt.–8.8	Exp. 4 Wt.–8.8	Exp. 1 Wt.–8.2	Exp. 2 Wt.–8.1	Exp. 3 Wt.–8.1	Exp. 4 Wt.–8.1
0	89.3	103.1	82.0	105.3	80.6	80.1	89.7	111.1
10	215.0	204.1	250.0	235.3	206.2	172.4	168.0	206.2
20	146.0	149.2	181.8	155.0	168.0	140.8	141.8	169.5
40	121.2	126.6	136.0	139.9	124.2	102.0	113.0	103.1
60	85.5	97.6	95.2	93.9	108.1	90.9	95.2	95.7
90	87.3	94.6	87.3	91.3	92.2	88.5	94.3	98.0
120	91.3	91.3	85.1	90.9	90.5	91.7	96.1	97.1
180	—	92.6	81.3	89.3	89.3	84.4	89.7	94.3

TABLE II.
Dog No. 2.
Blood Sugar in mg. per 100 cc.

	Controls			After Rt. Vagus Section			After Left Vagus Section		
Time (min.)	Exp. 1 Wt.– 10.4	Exp. 2 Wt.– 10.4	Exp. 3 Wt.– 10.2	Exp. 1 Wt.– 10.0	Exp. 2 Wt.– 10.0	Exp. 3 Wt.– 10.0	Exp. 1 Wt.– 9.0	Exp. 2 Wt.– 8.4	Exp. 3 Wt.– 6.9
0	93.0	90.1	87.3	92.6	85.1	90.9	93.0	85.8	88.5
10	215.0	241.0	238.1	204.1	186.9	243.9	—	—	198.1
20	175.4	186.9	173.9	165.3	140.0	161.3	180.2	186.0	175.4
40	104.2	102.6	93.0	117.6	—	101.5	138.9	133.3	135.1
60	79.0	80.6	71.2	93.9	84.7	81.0	124.2	98.5	117.6
90	83.3	88.5	90.5	78.7	86.2	84.0	104.2	82.3	103.1
120	87.7	100.5	86.5	72.7	90.1	90.5	94.3	77.8	105.3
180	88.5	95.7	87.7	77.8	96.6	80.6	77.5	76.3	80.0

TABLE III.
Dog No. 3.
Blood Sugar in mg. per 100 cc.

Time (min.)	Controls			After Bilateral Vagus Section			
	Exp. 1 Wt.–9.9	Exp. 2 Wt.–9.0	Exp. 3 Wt.–9.0	Exp. 1 Wt.–8.0	Exp. 2 Wt.–7.9	Exp. 3 Wt.–7.9	Exp. 4 Wt.–8.1
0	82.6	82.0	87.3	102.6	108.1	94.6	98.0
10	194.2	181.8	196.1	181.8	194.2	188.9	206.2
20	140.2	146.0	165.3	156.2	156.2	155.0	166.7
40	117.0	106.9	116.3	120.5	125.8	124.2	114.9
60	91.7	93.4	96.6	106.4	105.3	114.3	102.0
90	80.6	98.0	89.7	98.0	101.5	104.7	98.5
120	86.2	94.6	88.5	97.1	99.0	108.7	106.9
180	83.0	86.2	85.1	95.2	90.9	94.6	98.5

Effect of coeliac ganglionectomy following bilateral vagus section. In dog No. 4 in which bilateral vagus section had been performed, removal of the cœliac ganglia 13 months later had no effect on the glucose tolerance. The output of urinary sugar remained essentially unaltered. The results are shown in Table IV.

TABLE IV.
Dog No. 4.
Blood Sugar in mg. per 100 cc.

Time (min.)	Controls			After Bilateral Vagus Section			After Bilateral Coeliac Ganglionectomy		
	Exp. 1 Wt.–6.2	Exp. 2 Wt.–6.3	Exp. 3 Wt.–6.0	Exp. 1 Wt.–6.7	Exp. 2 Wt.–6.9	Exp. 3 Wt.–7.2	Exp. 1 Wt.–7.0	Exp. 2 Wt.–7.1	Exp. 3 Wt.–7.1
0	88.1	91.7	112.4	93.9	90.9	95.2	86.9	84.7	95.2
10	219.8	192.3	206.2	202.0	204.1	227.3	—	219.8	—
20	169.5	141.8	148.1	158.7	162.6	177.0	166.7	160.0	188.0
40	108.1	97.6	107.5	108.1	114.3	125.8	120.5	121.2	123.5
60	95.7	94.3	90.9	94.6	97.1	104.7	101.5	97.1	103.1
90	94.6	84.0	89.3	90.5	96.6	99.0	91.3	92.6	98.0
120	93.4	—	96.1	101.0	98.0	105.8	97.1	93.9	94.3
180	89.3	95.7	95.2	113.6	97.6	95.7	93.0	89.3	94.6

Effect of left adrenalectomy and right adrenal denervation. Following removal of one adrenal and denervation of the other in dog No. 5 the blood sugar after injection of glucose fell somewhat more rapidly than had been observed for the controls. The greatest departures from the control values occurred at the 20 and 40 minute points, the average difference being about 15 mg. for the former and 20 mg. for the latter. At points taken 60 and 90 minutes after injection, the blood sugar values averaged about 10 mg. lower than the controls. At the end of 2 hours, the values were essentially in agreement with those obtained before operation. While from this series of experiments there would appear to be some slight difference between the blood sugar curves of the

operated and the control animals, the difference, though consistent, is so small as to be of questionable significance, and insufficient for constituting a theoretical basis justifying this operative procedure as a means of increasing glucose tolerance. The output of urinary sugar was not materially altered after the operation.

The results are recorded in Table V.

Effect of coeliac ganglionectomy following left adrenalectomy and right adrenal denervation. The blood sugar values following bilateral cœliac ganglionectomy in dog No. 5 four weeks after removal of one adrenal and denervation of the other were found to agree essentially with those obtained for adrenal denervation. The output of sugar in the urine remained about the same.

The results following adrenal denervation and cœliac ganglionectomy are grouped in Table V.

TABLE V.
Dog No. 5.
Blood Sugar in mg. per 100 cc.

	Controls		After Left Adrenalectomy and Right Adrenal Denervation			After Bilateral Coeliac Ganglionectomy	
Time (min.)	Exp. 1 Wt.–6.5	Exp. 2 Wt.–6.8	Exp. 1 Wt.–6.6	Exp. 2 Wt.–6.5	Exp. 3 Wt.–6.5	Exp. 1 Wt.–6.5	Exp. 2 Wt.–6.8
0	80.0	111.1	74.3	82.3	75.2	74.3	75.7
10	202.0	198.1	—	230.0	204.1	204.1	210.5
20	160.0	152.7	146.0	151.5	131.6	111.1	137.5
40	117.6	111.1	95.2	96.1	87.7	83.7	73.5
60	93.9	93.4	79.0	88.5	79.4	85.5	82.0
90	93.9	90.9	80.0	88.9	78.1	88.1	78.1
120	97.1	86.2	87.3	88.5	82.0	80.6	85.5

The above findings confirm the results of cœliac ganglionectomy following double vagotomy in showing that removal of the sympathetic innervation has no appreciable effect on the glucose tolerance curve, although de Takats and Cuthbert[3] have been inclined to call differences similar to those obtained here as significant. In this paper these authors state that "the cœliac ganglion mediates nerve impulses, the exclusion of which brings about either an increased insulin production or a reduction in the insulin requirement." We are unable to confirm the above statement. In addition, the same authors write that "in preliminary tests adrenal denervation alone has given a marked rise in tolerance." Although we have observed some changes after adrenal denervation, we are inclined to minimize their importance.

[3] de Takats, G., and Cuthbert, F. P., *Am. J. Physiol.*, 1932, **102**, 614.

Summary. 1. Section of the vagus nerves below the diaphragm was found to have no effect on the tolerance of normal dogs to intravenously injected glucose. No evidence was obtained which pointed to secretory or tonic inhibitory fibers in either of the vagus nerves. 2. Removal of one adrenal and denervation of the other resulted in a slightly more rapid fall in blood sugar after intravenous injection of glucose. This difference in rate, though persistent in the animal studied, was nevertheless small and of doubtful significance. 3. Cœliac ganglionectomy after bilateral vagus section and after removal of one adrenal and denervation of the other was without effect on glucose tolerance. 4. No evidence was obtained in normal dogs to substantiate a theoretical basis for operative procedures designed to increase tolerance to glucose.

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Calorigenic Action of Methylene Blue During Muscular Exercise.*

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In previous communications (Rapport,[1] Canzanelli, Segal and Rapport[2]) we have presented evidence indicating that while the energy of the calorigenic action of certain substances, (such as protein, certain amino acids, thyroxine, etc.) can not be used as a fuel for muscular work, that of carbohydrate and fat could be so used. The present communication deals with similar observations in regard to methylene blue, a substance foreign to the body, which, when administered, has a considerable effect on the total metabolism.

The experiments were made on a single well-trained female dog, weighing about 9 kilos, and subsisting on a constant maintenance

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1 Rapport, D., *Am. J. Physiol.*, 1929, **91**, 238.

2 Canzanelli, A., Segal, M., and Rapport, D., *Am. J. Physiol.*, 1934, **110**, 410.