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BLOOD-SUGAR VARIATIONS IN NORMAL AND IN SYMPATHECTOMIZED DOGS

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In a previous publication [1936] we have stated that after various grades of exercise the blood sugar varies in the sympathectomized dog as it does in the normal dog. The result remains the same if after complete sympathectomy one adrenal is removed and the other demedullated. In all such dogs the blood sugar immediately after exercise varies within the same limits even though all known liberators of adrenine are eliminated. We have sought for clues to the nature of the regulatory mechanism in the reactions of the sympathectomized dog to various factors which affect the concentration of blood sugar. Details will be found in papers in the course of publication concerning the operations and the tests employed to demonstrate the completeness of sympathectomy.

I. Blood sugar after exercise

Table I shows a few values determined by the method of Folin & Malmros [1929] after different grades of exercise by the same dogs before and several weeks after complete sympathectomy. In these and in experiments to be described below the dogs had fasted from 12 to 16 hr.

II. Blood sugar after glucose ingestion

Glucose (2 g./kg. body weight) in 20 % solution was administered by a stomach tube. Blood was then collected from the saphenous vein at half-hourly intervals for 3½ hr. Fig. 1 shows the curves based on the average response of normal dogs and of dogs some weeks after sympathectomy. The peak of the mean curve for normal dogs is 134 and for the sympathectomized dogs, 141. Three of the normal dogs were below

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TABLE I

Dogs	Intensity of work kg.m./min./ kg. body weight	Duration of work min.	Blood sugar, mg./100 c.c. Before	After
	1. Normal dogs			
Abel	150	50	77	71
,,	175	25	78	85
Blacky	175	25	78	84
Redy	125	25	100	94
	2. Sympathectomized dogs			
Abel	150	50	79	73
,,	175	25	77	85
Blacky	175	25	79	86
Redy	125	25	92	88
	3. Sympathectomized, one adrenal out, the other demedullated			
Abel	150	50	79	68
Bull	100	25	79	81
,,	100	50	78	62

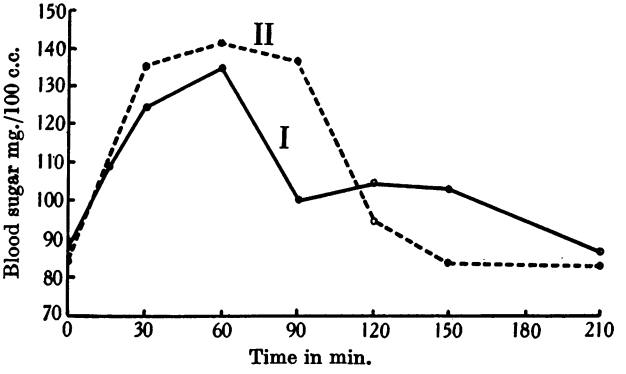

Fig. 1. The average results of glucose-tolerance tests on six normal dogs (I) and on eight sympathectomized dogs (II). In this figure and in Figs. 3 and 4 glucose was administered at zero time.

these two maxima and three were above. Of the sympathectomized, four were below and four above. There is no evidence in our data which would indicate that the two groups differ significantly in their response to glucose ingestion.

III. BLOOD SUGAR AFTER ADRENALINE INJECTION

Adrenaline (Parke Davis & Co.) was injected subcutaneously (0·1 mg./kg. body weight in 0·05 % solution). The average curves in Fig. 2, showing blood sugar following the injection of adrenaline in the normal and in the sympathectomized dogs, are much alike. Mean values in twelve experiments on nine normal dogs show a maximum of 149 mg./100 c.c. after 150 min. In twelve experiments performed on eight dogs

several weeks after sympathectomy, the mean peak of 148 mg./100 c.c. is reached in 120 min. While there are large differences in the response of individual dogs to adrenaline, these do not seem to depend on sympathectomy.

Four adrenaline experiments were carried out on two dogs having an intact autonomic nerve supply but with one adrenal removed and the other demedullated. The responses were within the normal range. Although the mean curve for blood sugar was slightly higher than those shown in Fig. 2 (maximum 172 mg./100 c.c.), the difference is of doubtful significance. The same conclusion was reached from the study of two dogs that were totally sympathectomized and also deprived of one adrenal and the medulla of the other.

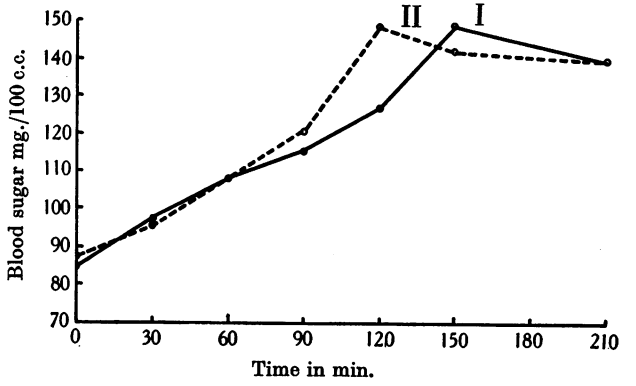

Fig. 2. The average blood-sugar curves after adrenaline injection at zero time in twelve experiments on nine normal dogs (I) and in twelve experiments on eight sympathectomized dogs (II).

These observations, like those referred to above, reveal no difference between normal and sympathectomized dogs with respect to blood-sugar regulation, provided some weeks are allowed for recovery. It does not follow that the regulation of blood sugar is independent of the sympathetic nervous system. On the contrary, we have found that in some dogs soon after sympathectomy the responses to sugar-tolerance tests and to adrenaline are abnormal and furthermore that sensitivity to insulin, first shown by Dworkin in the sympathectomized cat [1931], remains undiminished even $3\frac{1}{2}$ years after sympathectomy.

To illustrate the first of these points we may refer to some experiments on Foxie. Sympathectomy was performed in three stages. Fourteen days after completing the last stage the blood sugar, after a standard glucose-

tolerance test, rose from 92 to 244 in 60 min. (Fig. 3); it had not quite returned to the initial value after 150 min. Before sympathectomy the increase had been from 72 to 150 in 60 min. and the original level was reached within 150 min. Three weeks after sympathectomy the increase was from 87 to 247, while two weeks later the original response was

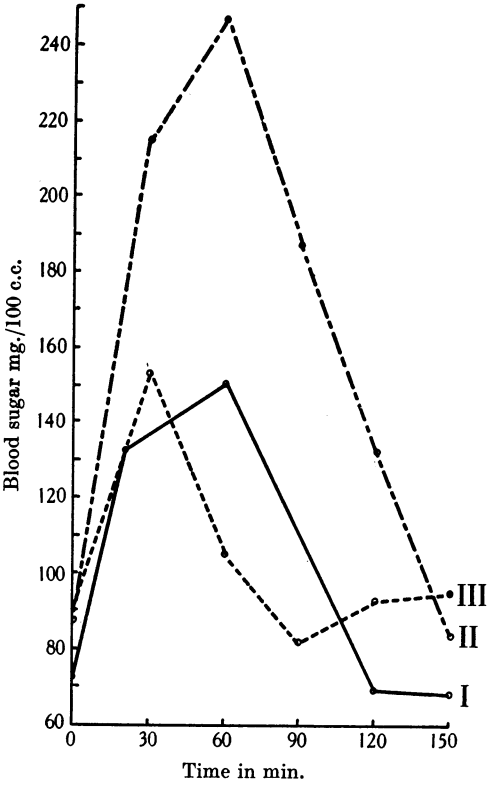

Fig. 3. Glucose-tolerance tests on Foxie in the normal state (I), 14 days after sympathectomy (II), and 32 days after sympathectomy (III).

exhibited. These results suggest that blood-sugar regulation is disturbed by sympathectomy and that more than 3 weeks may be required to regain the normal response to sugar ingestion. These experiments and others of the same character are summarized in Table II. The inadequacy of blood-sugar regulation just referred to was not seen in the case of Blacky; it certainly is not a universal, and it may not be a general phenomenon. Whether the control of blood-sugar concentration after excessive ingestion of glucose depends on mechanisms operative in the normal dog,

TABLE II. Sugar-tolerance tests in normal and sympathectomized dogs (2 g./kg.)

Dogs	State	Days after operation	Blood sugar, mg./100 c.c.		Time at which maximum is attained min.
			Control	Maximum	
Foxie	Normal	—	72	150	60
	Sympathectomized	14	92	244	60
		21	86	247	60
		38	85	150	30
		40	90	152	30
	Sympathectomized + adrenalectomized	18	81	167	30
	,,	23	84	174	60
	,,	42	94	132	60
Niobe	Sympathectomized	14	100	196	90
Blacky	Normal	—	73	143	90
	Sympathectomized	14	83	117	90
		29	81	124	60
Mary	Normal	—	81	135	15
Ike	,,	—	76	101	15
Bull	Sympathectomized	20	87	120	60
S I	,,	15	86	178	90
S II	,,	29	83	132	60
	(Adrenaline test preceding day)				
Redy	Normal	—	100	161	60
Winnie	,,	—	98	152	60
Dirty	Sympathectomized	20	81	147	90
Helen	Normal	—	94	200	60
Abel	Sympathectomized	700	90	230	60
Yellow	,,	18	85	282	90
Sheba	Adrenals out	30	82	204	60
Redy	Sympathectomized	17	93	204	90
Isabel	Normal	—	72	227	60

or whether some vicarious device comes into play, as in cardiac acceleration, remains to be determined. It is unlikely that the eventual return of the sugar-tolerance test to normal can be ascribed to nerve regrowth or adrenine liberation, for the same response is obtained in dogs that are sympathectomized as in those deprived of one adrenal and the medulla of the other.

The response to adrenaline injections also is indicative in some instances of a slow re-establishment of homoeostatic control after sympathectomy. In Foxie the response was still far from normal 40 days after the operation; blood sugar increased only about one-half as much as before the operation (Fig. 4). No more tests were carried out on this dog, but others, sympathectomized for periods varying from 1 month to 2 years, whether with or without the adrenal medulla, exhibited the normal response to adrenaline injection.

It was discovered that the injection of adrenaline may influence the outcome of a sugar-tolerance test carried out on the following day. Foxie

had an adrenaline injection on the 17th day after sympathectomy and on the following day her maximal rise in blood sugar in the tolerance test was only about one-half as great as 4 days before. Possibly the injection of adrenaline, by producing hyperglycaemia, causes a rise in insulin production sufficiently prolonged to alter the rate of glycogen deposition 24 hr. later. We have not determined whether or not this phenomenon is peculiar to the sympathectomized dog.

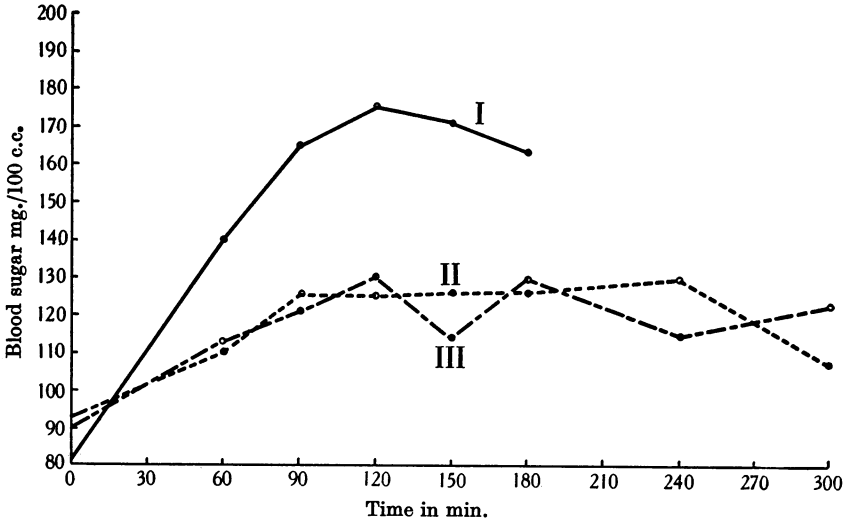

Fig. 4. Blood-sugar curves on Foxie after adrenaline injection at zero time before (I), 22 days after (II), and 40 days after sympathectomy (III).

IV. Blood sugar after insulin injection

In normal dogs the subcutaneous injection of 4 units of insulin per kg. body weight produces a marked drop in the blood sugar. The average curve for three dogs reaches a minimum of 40 mg./100 c.c. an hour afterwards (Fig. 5), remains low for about 1 hr., and then slowly rises. Under these conditions dogs do not look happy, but in our experience they have no convulsions and come back to normal without any treatment.

The sympathectomized cat, as shown by Dworkin [1931], is much more sensitive to insulin than the normal cat. This is also true of the dog. One unit of insulin per kg. body weight produces in a totally sympathectomized dog a very marked drop in the blood sugar. The mean curve on four dogs reached 36 mg./100 c.c. after 60 min., 32 an hour later. Within

the next half hour, all the animals had severe convulsions; glucose was injected in order to revive them.

Here again we performed some experiments on two dogs with their sympathetic nervous systems intact, but with one adrenal removed and the other demedullated or denervated. Two other dogs were totally sympathectomized, with one adrenal removed and the other demedullated. The reaction to insulin is like that in the sympathectomized dog:

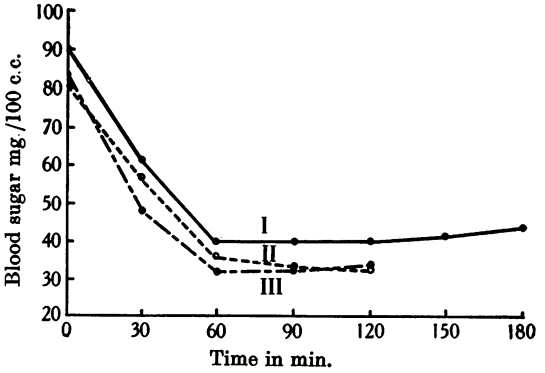

Fig. 5. The average blood sugar in three normal dogs after the injection of 4 units of insulin per kg. at zero time (I), in three sympathectomized dogs after 1 unit (II), and in two dogs with one adrenal removed and the other demedullated after 1 unit (III).

one unit of insulin always produces a marked fall of the blood sugar, with hypoglycaemic convulsions; four times this dose in normal dogs has less serious consequences. The fact that the sensitivity to insulin does not require the complete removal of the sympathetic system, but merely removal of the adrenal medulla (Fig. 5), indicates that in this instance sympathectomy may be effective only because it involves the denervation of the adrenals. With the dogs deprived of nervous control of adrenine and sympathin liberation, the capacity for antagonistic response to insulin is greatly reduced.

Discussion and conclusion

When sympathectomized dogs, with or without the adrenal medulla, recover from the operation, the regulation of the blood sugar during exercise, after ingestion of glucose and after adrenaline injection, is normal, even though no adrenine or sympathin can be liberated. Since any possible interaction between adrenine and insulin is eliminated, the phenomenon may mean that the liver liberates sugar when the sugar level in the blood drops. In other words, the amount of sugar in the

blood may be the factor which regulates its release from the liver. Or, it may be that the factor of the pituitary, reported by Houssay [1936] to be concerned in regulation of blood sugar, is elaborated fast enough to maintain a normal blood sugar in the exercise experiments.

The continued marked sensitivity to insulin can be explained if one assumes that, when an excess of insulin is to be dealt with, the removal of sugar from the blood is so fast that mechanisms available for the mobilization fail to keep pace; in this circumstance, perhaps, the proper balance cannot be maintained in the absence of adrenine.

We conclude that after total sympathectomy, with or without removal of the adrenal medulla, dogs are able to regulate their blood sugar within normal limits during and after exercise, after glucose ingestion and after adrenaline injection, provided adequate time is allowed for recovery from the operation. Sympathectomized dogs remain sensitive to insulin indefinitely; this incapacity to cope with an abnormal emergency is dependent merely on denervation of the adrenal glands, since dogs deprived of the adrenal medulla are as sensitive to insulin as totally sympathectomized dogs.

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