THE INFLUENCE OF THE VAGUS ON THE ISLETS OF LANGERHANS. Part I. Vagus hypoglycæmia.

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ALLEN(1) has shown that sugar tolerance in the dog is not lowered when a sufficient pancreas graft in the spleen is separated from all original connections other than its duct, while investigations of Banting and Gairns(2) also indicate that the secretion of insulin is not necessarily dependent on the nerve supply to the islets of Langerhans and is normally a continuous process. Nevertheless, it is not unreasonable to suppose that the nervous system may influence the secretion of insulin. The general physiological antagonism between sympathetic and parasympathetic systems suggests the possibility of some mechanism controlled by the parasympathetic to counteract the hyperglycæmia produced by sympathetic activity. Eppinger and Hess state that pilocarpine can arrest adrenaline hyperglycæmia(3) and that atropine in certain cases may cause glycosuria(4). These phenomena are explicable if it can be shown that stimulation of the parasympathetic will produce an increase of insulin in the blood. The nerve-supply to the islets of Langerhans is conveyed mainly, if not entirely, in the right vagus and Macleod and his co-workers(5) have produced hypoglycæmia by stimulation of the right vagus in the neck. Indirect evidence of a nervous factor causing hypoglycæmia was given in a recent paper(6), where it was shown that guanidine will produce in rabbits an immediate fall in blood-sugar if sympathetic glycogenolysis is prevented by ergotoxine, or if the animal's glycogen store has been previously depleted. This hypoglycæmic action was found to be inhibited by atropine. In the present paper more direct evidence is offered of the influence of the vagus on the secretion of insulin.

As in the previous investigation(6), Bang's old micro-method for the estimation of blood-sugar was used, blood being obtained from an ear vein. The normal blood-sugar content was determined immediately before an experiment by three estimations at intervals of half an hour.

All drugs were administered intravenously and food was withheld from an animal for 18 hours before any experiment.

Effect of pilocarpine. In view of the effects of guanidine referred to above, it was anticipated that any drug stimulating the parasympathetic would, under suitable conditions, produce a lowering of blood-sugar. Each of three rabbits was therefore given 3 mgms. of ergotamine tartrate followed one hour later by pilocarpine nitrate in ·5 p.c. solution; No. 1 received ·5 mgm. per kilo; No. 2, ·75 mgm. per kilo; and No. 3, 1 mgm. per kilo. In all three cases a fall in blood-sugar resulted, that in No. 3 being approximately of the same order as that produced by ·5 gm. guanidine hydrochloride per kilo (Table I). It has recently been stated that ergotamine alone will lower the blood-sugar of normal rabbits (7). In numerous control experiments I have found no change in blood-sugar level within an hour of the intravenous injection of 3 mgms. ergotamine tartrate and in two cases in which estimations were made over a period of five hours after ergotamine alone the following values were found:

Hours after injection	0	½	1	1½	2	2½	3	3½	4	4½	5
	·124	·122	—	·120	·120	—	·118	·118	—	·116	—
	·120	—	·124	—	·128	—	·118	·116	·114	—	·120

It is evident then that ergotamine cannot be responsible for the immediate fall in blood-sugar when this drug precedes the administration of pilocarpine or guanidine. This is also shown by the fact that pilocarpine alone in doses of 1 mgm. per kilo lowers blood-sugar (Table I).

TABLE I.

Hours after injection	Guanidine ·5 gm. per kilo	Pilocarpine: After ergotamine 3	After ergotamine 2	After ergotamine 1	Pilocarpine: Alone 4	Alone 5
0	·120	·105	·110	·124	·120	·120
½	·112	·090	·097	·110	·100	·100
1	·096	·083	·090	·102	·086	·092
1½	·090	·080	·085	·105	·092	·110
2	·092	·085	—	·110	·107	·115
2½	·105	—	·096	—	·109	—
3	·110	·100	·102	·124	—	·122

Guanidine after vagotomy. Direct evidence of the influence of the vagus in producing hypoglycæmia was sought by investigating the effect of guanidine hydrochloride on the blood-sugar in rabbits in which this nerve was divided in the neck. The operation was performed on the right vagus in six animals, the hypoglycæmic action of guanidine having previously been determined in two of them. (It may here be recalled that in an intact rabbit a second dose of guanidine preceded by ergota-

mine almost invariably produces a greater fall in blood-sugar than the first, even when an interval of several weeks intervenes between the doses (6).) Two weeks after section of the vagus in the case of No. 4 and No. 5, three in the case of No. 6 and No. 7, four in the case of No. 8 and five in the case of No. 9, 3 mgms. ergotamine tartrate were given, followed one hour later by ·1 gm. guanidine hydrochloride per kilo. It will be seen that in one case only did hypoglycæmia result (Table II).

TABLE II.

Hrs after injection	Before vagotomy		After vagotomy (right side)					
	4	5	4	5	6	7	8	9
0	·122	·112	·125	·132	·115	·117	·110	·125
½	·091	·085	·122	·128	·120	·115	·108	·120
1	·076	·068	·124	·136	·110	·115	·105	·101
1½	·085	·075	·128	·134	·121	·117	·100	·074
2	·095	·095	·124	·130	·132	—	—	·076
2½	—	—	—	—	·128	·125	·110	—
3	·110	·105	·118	·125	·125	—	—	·084
3½	—	—	—	—	—	·127	·110	—
4	·116	·114	·128	·125	·115	—	—	·090

In two animals the left vagus was resected in the neck, the normal reaction of the blood-sugar to guanidine having been previously determined in one of them. Two weeks after the operation in one case and three weeks in the other ·1 gm. per kilo of guanidine hydrochloride, preceded by 3 mgms. ergotamine, was injected, with the result that one rabbit showed no alteration in blood-sugar while a hypoglycæmia occurred in the other as shown below.

Hrs after injection	0	½	1	1½	2	2½	3
Before vagotomy No. 10	·115	—	·085	·080	·090	·103	—
After „ „ 10	·100	·077	·070	·068	·080	·090	—
„ „ „ 11	·116	·110	·116	·114	—	—	·120

Guanidine has been shown to stimulate the preganglionic fibres of the vagus (8), and the above results may thus be interpreted as indicating that in the majority of rabbits the right vagus in the neck carries fibres, stimulation of which causes a lowering of blood-sugar, but in some cases these fibres appear to be carried in the left vagus.

Guanidine and "Infundin." That increased liberation of insulin is responsible for the hypoglycæmia produced by vagal stimulation is suggested by two experiments based on the observation of Burn that pituitary extract diminishes or abolishes the hypoglycæmia normally brought about by insulin (9). Each of two rabbits was given a preliminary injection of ergotamine, followed one hour later by ·1 gm. guanidine hydrochloride and 1 c.c. "Infundin" (Burroughs, Wellcome and Co.) per

kilo. It is seen from Table III that although "Infundin" alone and guanidine alone (ergotamine having been previously given in each case) cause a definite fall in blood-sugar, the same amounts of each given simultaneously have much less effect on the blood-sugar in one rabbit and practically no effect in the other.

TABLE III.

Hrs after injection	"Infundin"		Guanidine		Guanidine and "Infundin"	
	No. 3	No. 12	No. 13	No. 3	No. 13	No. 3
0	·105	·110	·110	·120	·110	·120
½	·085	·104	·080	·095	·105	·118
1	·065	·092	·070	·080	·100	·110
1½	·070	·075	·065	·082	·094	·112
2	·075	·070	—	—	·090	—
2½	—	—	·070	—	—	·112
3	·080	·075	·075	—	·105	—
3½	—	—	—	·085	·110	·117
4	·085	—	·090	·095	·105	—

It is of interest to note that the mixture of guanidine and "Infundin" appeared to be particularly toxic in the case of No. 12 (an old rabbit) which after a preliminary few moments of intense excitement became comatose and was killed. The youngest of the three (No. 3) showed no untoward symptoms, while No. 13 after a few minutes of mild excitement appeared normal. It may seem possible that the antagonism shown in these experiments is one between pituitary extract and guanidine and not pituitary extract and insulin, but in view of the symptoms shown by the animals this is improbable, and in the absence of blood-sugar estimations, mere observation would have suggested that "Infundin" facilitated guanidine intoxication.

Glucose tolerance after vagotomy. As a sequence of the foregoing results, the question naturally arose whether the vagus normally exerts any control on the sugar content of the blood. If it does, the glucose tolerance of animals might be expected to be altered after vagotomy. In Table IV are given blood-sugar values found at half-hourly intervals following the intravenous injection of 1 gm. of pure glucose per kilo of body-

TABLE IV.

Hrs after injection	Before vagotomy			After vagotomy		
	No. 14	No. 15	No. 16	No. 14	No. 15	No. 16
0	·120	·122	·122	·120	·122	·126
½	·315	·305	·315	·282	·285	·264
1	·154	·178	·225	·214	·145	·122
1½	·137	·150	·116	·125	·125	·124
2	·118	·125	·122	·116	·122	·120
2½	—	—	—	·120	—	—

weight in rabbits before and two weeks after section of the right vagus in the neck. The glucose was given in 10 p.c. solution at the rate of 10 c.c. in 3 minutes.

The lower sugar value found half an hour after injection in the animals after vagotomy compared with the corresponding observation before vagotomy is apparently of no significance, as a similar phenomenon was observed in a second tolerance test on normal rabbits. It is evident then that this test gives no indication of altered sugar tolerance after vagotomy. Similarly, no alteration was found in three rabbits that had been given ·2 mgm. atropine sulphate per kilo 15 minutes before the sugar injection. These results were to be expected in view of the findings of Allen(1) and of Banting and Gairns(2).

Discussion.

The significance of the nerve supply to the islets of Langerhans is obscure. That a ready supply of insulin is necessary to deal with a sudden increase in blood-sugar is apparent in that continued hyperglycæmia can produce atrophy of islet tissue, and again, in the absence of islet tissue hyperglycæmia is practically limited by the relation of excretion to production and ingestion of glucose. All available evidence indicates that increase in blood-sugar is itself a sufficient stimulus for the production of insulin. It is possible that the action of the vagus on the islet cells is merely secondary to alteration of the blood supply. Banting and Gairns(2) have shown that increase in blood-flow to the pancreas causes an increase in the insulin output. If vagal hypoglycæmia is due to vasodilatation in the pancreas some difference might be expected in the action of pilocarpine in lowering blood-sugar when given alone and when the sympathetic system is depressed by ergotamine. Table I, however, indicates no obvious difference. It is difficult to believe that the vagus supply to the islets is functionless and the possibility must be considered that the influence is similar to that of the fibres supplying the acinar cells. Mellanby(10) has shown that when the enzyme content of pancreatic juice, stimulated to flow by secretin, has fallen to a low level it may be raised to its original value by vagal stimulation, which appears to facilitate the manufacture of enzymes by the acinar cells. If the vagus supply to the islets has a similar function it ought to be easier to exhaust the islets in an animal with the vagus cut than in a normal animal. The glucose tolerance test described above gives no indication of this, but tends to show that sufficient insulin can be produced to meet an emergency without vagal control. This aspect of

the problem is at present the object of further investigation. Whatever may be the mode of action of the vagus in the foregoing experiments, the results suggest that caution may be necessary in the administration to diabetics or potential diabetics of drugs which stimulate the vagus.

SUMMARY.

In the rabbit, drugs which stimulate the parasympathetic system cause a lowering of blood-sugar under the conditions described. This effect is not produced after section of the right vagus in the great majority of rabbits; it may be prevented in some animals by section of the left vagus.

The results described suggest that stimulation of the vagus causes a secretion of insulin.

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