followed by a comparable elevation of clearance accompanied by an increase both in the filtered load and the amount absorbed by the tubules. Data indicated that the tubular absorption of citric acid was not reduced by ascorbic acid. Administration of potassium did not increase the citrate clearance.

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Effect of Histamine and Histamine Liberator, Compound 48/80, on Blood Glucose.* (23721)

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The relationship between adrenal glands and the action of histamine was first revealed by Dale(1) who showed that small doses of histamine produced dilatation of the sensitized pupil of the cat similar to the dilatation produced by small doses of epinephrine. Burn and Dale(2) established that the secondary rise in blood pressure in the cat following injection of histamine was abolished by removal of the adrenals. Histamine injected in small amounts (1 μg or less) into the arterial blood supplying the adrenal gland of the cat is known to liberate epinephrine as judged by pressor responses and retraction of the nictitating membrane(3,4). Another more sensitive index of the action of injected or liberated epinephrine is the hyperglycemia resulting from the known glycogenolytic activity of this substance. Histamine injected intravenously into dogs, rabbits and rats(5,6,7) has been reported to produce hyperglycemia which is presumably due to liberated epinephrine. In some of the studies involving hyperglycemic responses in the dog and rabbit rather large doses of histamine have been used, and the rise in blood glucose could result from direct stimulation of the adrenal medulla by injected histamine and/or from reflex sympathetic activity coincident with severe shock. Experiments were therefore made in unanesthetized dogs and rabbits using several doses of histamine to determine whether a graded hyperglycemia could be demonstrated in the absence of moderate or severe grades of shock. In another series of experiments, compound 48/80 which is designated as a potent liberator of endogenous histamine(8). was employed in a similar manner for the purpose of comparing the 2 substances with respect to possible hyperglycemic activity.

Methods. In the histamine series, trained male albino rabbits weighing 3 to 4 kg were fasted 18-20 hours. Blood samples were taken from each animal 3 to 5 minutes before the injection of saline or histamine diphosphate and again after 15 to 60 minutes. Controls received physiological saline, while test animals received 0.1, 0.15 and 0.2 mg/kg of histamine in terms of the base. Higher doses of 0.25 and 0.3 mg/kg proved to be lethal in several instances. Each control and experimental group comprised 9 to 11 animals. In addition, each of 4 trained mongrel dogs, fasted approximately 20 hours, was injected

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TABLE I. Influence of Histamine and Compound 48/80 on Blood Glucose (mg %) of Trained Rabbits.

Dose, mg/kg intrav.	Preinj. level	Min. after inj. 15	20	30	60
		I. Histamine (base)			
.1	90 ± 2.2*	96 ± 4.3	94 ± 4.7	90 ± 4.1	99 ± 6.6
.15	94 ± 2.1	98 ± 5.5	99 ± 7.3	97 ± 4.7	101 ± 4.0
.2	93 ± 2.0	100 ± 6.1	105 ± 6.1	110 ± 6.7†	106 ± 4.8†
		II. Compound 48/80			
.5	‡115 ± 3.7	120 ± 8.5	119 ± 8.7	116 ± 10.2	115 ± 11.0
	§120	152	154	156	162
	§123	134	134	132	121

* Each value represents mean ± stand. error of 9-11 animals.
† $P < .05$ indicating a statistically significant change.
‡ Each value represents mean ± stand. error of 6 animals.
§ Individual values for 2 animals in this group showing toxic symptoms.

twice on different occasions with physiological saline and twice with each of 3 doses of histamine equivalent to 0.05, 0.1 and 0.2 mg kg of the base. Blood samples were taken 3 minutes before and at 10 to 60 minutes after injection. In experiments with compound 48 80, trained male albino rabbits were treated as in the histamine group. Each control and test group comprised 5-6 animals, controls receiving saline and test groups 0.3 or 0.5 mg kg of 48 80. Trained mongrel dogs also received saline or 48/80 (0.1 and 0.5 mg kg), each control or experimental group comprising 6 to 7 animals. Blood samples were collected as described above. Injections were made intravenously during 10 seconds in volume of 0.5 to 1.0 ml. Blood glucose was determined by semi-micro technic of Folin-Malmros(9).

Results. Histamine. In rabbits we demonstrated a graded hyperglycemia following histamine. At highest dose of 0.2 mg kg many animals manifested moderate to severe grades of shock and in these cases a moderate hyperglycemic response was evident (Table I). In dogs, a dose of 0.2 mg/kg histamine base caused a significant increase in blood sugar (Table II). This dose induced urination, salivation, lacrimation and tenesmus in each dog. Two animals collapsed and exhibited labored respiration. Lower doses of 0.05 and 0.1 mg kg produced milder responses but failed to raise the blood sugar level.

Compound 48/80. In 6 rabbits, a relatively high dose of this compound (0.5 mg/kg) produced no significant change in blood glucose except for a slight hyperglycemia (Table I) in 2 animals manifesting toxic symptoms of mild dyspnea, cyanosis and thrashing about. A dose of 0.3 mg/kg in 6 other animals produced no symptoms and no change in blood glucose. Six dogs which received 0.1 mg/kg, exhibited no significant changes in blood sugar. The animals reacted with shaking of head, rubbing head against floor and scratching of neck, for approximately 20 minutes. In 7 dogs receiving 0.5 mg/kg, symptoms consisted of shaking of head, ataxia, urination, defecation, and complete prostration. The animals usually recovered but were still unsteady at the end of the hour. A moderate fall in blood glucose was observed at 10 and 20 minutes after injection. At 60 minutes the level had increased 11 mg % above the control value (Table II). Thus compound 48/80 induced a slight transient hypoglycemia in the dog at a time when histamine shock induced a hyperglycemia.

Discussion. Histamine in minute quantities has direct epinephrine releasing action on the cat adrenal gland(1-4). This finding may be construed to mean that hyperglycemia previously reported to occur in dogs and rabbits after intravenous injections of histamine may also be due to a direct effect of histamine on the adrenal medulla. In our experiments small doses of histamine which produced mild symptoms in the dog and rabbit failed to raise the blood sugar level, whereas a moderate degree of hyperglycemia was induced when the dose was high enough to produce toxic effects.

The studies with 48/80 in rabbits revealed that the larger dose of 0.5 mg/kg was mildly toxic for 2 of 6 animals and in these instances

TABLE II. Comparison of Effects of Histamine and Compound 48/80 on Blood Sugar (mg %) of Trained Dogs.

Drug	Dose, mg/kg intrav.	Preinj. level	Min. after inj. 10	20	60
Histamine	.05	79 ± 2.6	84 ± 4.3	81 ± 3.3	84 ± 4.2
	.1	81 ± 3.8	87 ± 6.2	86 ± 6.2	84 ± 6.0
	.2	82 ± 3.5	92 ± 5.7*	98 ± 5.5*	91 ± 5.5*
48/80	.1	87 ± 3.3	84 ± 5.5	83 ± 5.6	84 ± 3.4
	.5	89 ± 2.7	75 ± 3.1*	82 ± 2.3*	100 ± 4.8*

Each value for histamine group is mean ± stand. error of 8 observations in 4 animals; for 48/80, mean ± stand. error of 6 to 7 animals (one observation/animal).

* P value $<.05$.

an actual hyperglycemia developed. However, analysis of the results for the whole group receiving this dose showed no significant changes. There was an indication therefore that compound 48/80, like histamine, did not induce hyperglycemia in rabbits unless it produced symptoms of toxicity.

The effect of 48/80 in dogs presented an entirely different picture. During histamine shock, a marked hyperglycemia develops 20 to 30 minutes after injection(5). In our studies, it was found that a moderate increase in blood glucose was manifest 10 and 20 minutes following injection of 0.2 mg/kg of histamine base. When compound 48/80 was administered at a dose level (0.5 mg/kg) capable of producing many severe symptoms including prostration in 6 of 7 animals, it induced, instead of a rise in blood sugar, a moderate hypoglycemia in 10 minutes during height of symptoms, still present but less pronounced in 20 minutes. A mild hyperglycemia was then observed at the end of an hour. These developments are the reverse of what would be expected from a potent histamine liberator especially in the dog in which compound 48/80 is known to release large amounts of histamine almost immediately. Since the effects of this compound on blood glucose are not consistent with those following histamine shock, it appears that 48/80 possesses some transient hypoglycemic activity in the dog unrelated to release of endogenous histamine. Such activity is apparently of sufficient magnitude to override any hyperglycemic response from reflex sympathetic activity called into play by the shock-like state induced by 48/80. The secondary mild hyperglycemia which was observed at the end of an hour may be a late manifestation of epinephrine release.

Summary. It was not possible to induce hyperglycemia in dogs and rabbits with nontoxic doses of histamine injected intravenously, whereas a moderate hyperglycemia occurred in both species when the dose was high enough to produce toxic effects; epinephrine release and glycogenolysis probably resulted from reflex sympathetic activity consequent to the shock induced. Compound 48/80 also did not induce hyperglycemia in rabbits except in those showing toxic symptoms. In the dog, a dose of 48/80 capable of producing severe symptoms, including prostration, caused a moderate fall in blood glucose at a time when histamine shock produced a hyperglycemia. Therefore, compound 48/80 exerted a transient hypoglycemic action in dogs which appears to be unrelated to histamine release.

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