

## Relationship Between Maximum Bicarbonate and Maximum Acid Outputs in the Dog.\* (31730)

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The normal human stomach produces several liters per day of gastric juice of pH about 1, yet the pH in the post-bulbar duodenum normally remains neutral(1). Gastric acid juice is neutralized by food, antral, duodenal, and jejunal secretion, bile and pancreatic juices. The normal human pancreas probably produces about one liter a day of juice of pH about 8. The quantities of the other fluids are uncertain.

The size of the stomach and the parietal cell mass vary in different individuals, as determined by actual parietal cell counts at post-mortem(2) or measurements of "maximum" acid output (M.A.O.), [the maximum histamine response (correlated with parietal cell mass)(3,4)]. Similarly the pancreas varies in size in different animals, as do measurements of maximum bicarbonate output (M.B.O.)(5).

We have tried, in dogs, to determine whether the M.A.O. and M.B.O. are of similar order of magnitude, and whether the size of doses of secretory stimulant to elicit maximum response of the stomach and of the pancreas are comparable.

*Method.* In each of 5 female dogs at laparotomy under general anesthesia the accessory pancreatic duct was tied and cut and a chronic Thomas-type duodenal fistula prepared. The dog was trained to stand in a Pavlov frame, and a month after operation pancreatic secretion was collected by cannulation of the main pancreatic duct through the Thomas fistula. The maximum alkaline (bicarbonate) output of the pancreas was determined for each dog in response to in-

travenous infusions of secretin (Vitrum)(5) and expressed as mEq  $\text{HCO}_3^-$ /15 min. At a second laparotomy under general anesthesia, a gastrostomy was constructed with a nylon cannula. Not less than 4 weeks after this second operation, the maximum histamine response of the stomach was determined by a modification of Marks, Komarov and Shay's (4) adaptation of Kay's augmented histamine test(6) to the dog. Before each test the dog was fasted for 16 hours, and on the morning of each test basal secretion was collected for 60 minutes or until minimal. Diphenhydramine (Benadryl) 20 mg was given intramuscularly and 20 minutes later histamine acid phosphate (histamine phosphate, U.S.P.) injected subcutaneously into the lumbar area. Ten-minute collections of gastric juice were then made for 90 minutes or until the stimulated secretion had ceased. The volume of each specimen was measured to the nearest 0.1 ml and the acidity determined by titration with 0.1 NaOH to pH 7.0 using phenol red as indicator. The acid output was then calculated for each period. The peak acid output in response to each injection of histamine was taken to be the peak 20-minute output (output over the peak consecutive 2 ten-minute collections). Different doses of histamine acid phosphate over the range 0.4 to 3.2 mg/kg were used on different days and dose-response curves constructed for each dog. The highest mean peak acid output (mEq/20 min.) was read from the graph and considered to represent the maximum acid output (M.A.O.) of that dog.

*Results.* The results in the 5 dogs are shown in Table I and Fig. 1. The M.B.O. (recalculated as mEq  $\text{HCO}_3^-$ /hr) expressed as a proportion of the M.A.O. (recalculated as mEq HCl/hr) ranged from 19 to 45% (mean 30%). In this series there was no significant correlation between M.B.O. and M.A.O. (Fig. 1). Dogs requiring the highest doses of

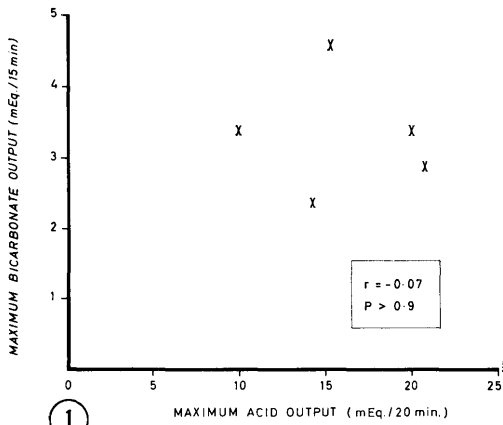
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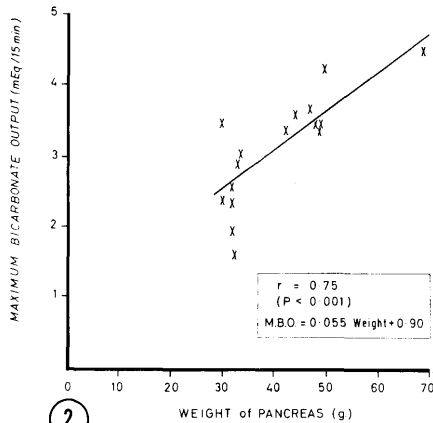
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TABLE I. Maximum Bicarbonate Output of Pancreas in Response to Secretin and Maximum Acid Output of the Stomach in Response to Histamine in 5 Female Dogs.

Dog	Body wt (kg)	Maximum bicarbonate output		Secretin dose (units/min)	Maximum acid output		Dose of histamine acid phosphate (mg/kg)	M.B.O./hr	
		mEq/15 min	mEq/hr		mEq/20 min	mEq/hr		M.A.O./hr	
3151	20.2	4.59	18.36	12	15.31	45.93	2.4	40.0	
2732	18.6	2.91	11.64	>16	20.85	62.55	1.6	18.6	
2796	20.6	3.40	13.60	8	10.11	30.33	1.6	44.8	
3270	23.0	2.39	9.56	12	14.38	42.14	1.2	22.7	
3308	20.6	3.37	13.48	8	20.11	60.33	2.2	22.3	



1



2

FIG. 1. Relationship between maximum bicarbonate output of the pancreas and maximum acid output of the stomach in 5 female dogs.

FIG. 2. Relationship between maximum bicarbonate output (M.B.O.) of pancreas and weight of pancreas in 16 Female dogs. Data of Baron and Perrier, and Hansky, Tiscornia, Dreiling and Janowitz(12).

secretin for M.B.O. were not those requiring the highest doses of histamine for M.A.O.

*Discussion.* In dogs the maximum histamine response is correlated with the parietal

cell mass(4), and we have shown that this maximal bicarbonate output of the pancreas is correlated with the weight of the pancreas (Fig. 2).

The present study has shown that the dog's pancreas can secrete about one-third as much alkali (mEq per mEq) as its stomach can secrete acid.

While the M.A.O. in man has been extensively studied, the maximum bicarbonate output has only recently been attempted(7,8). Even with a submaximal standard dose of secretin (Lilly, 1 unit/kg body weight) peak 15-minute bicarbonate output averaged in our hands 7.5 mEq (range 6-13 mEq)(9) which was similar to our peak 15-minute acid output in man after maximal dose of histamine: 6 mEq (range 1-13 mEq)(10).

*Summary.* The maximum bicarbonate output (M.B.O.) of the pancreas in response to secretin and the maximum acid output (M.A.O.) of the stomach in response to histamine have been studied in 5 dogs. The M.B.O. represents mEq for mEq about 30% M.A.O. Calculations from published human data suggest that the pancreas could neutralize the acid output of a normal stomach.

*Addendum.* Since this paper was prepared, Preshaw and Grossman(11) have reported that the mean maximal rate of secretion of bicarbonate by the dog's pancreas is about one-third of the mean maximal rate of acid secretion by the stomach.

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### An Adrenergic Substance in the Blood of Alloxan Diabetic and Acetoacetate Injected Rabbits.\* (31731)

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Sirek *et al* (1), making use of the observation of Ellis and coworkers(2) that dihydroergotamine can block the hyperglycemic effect of adrenaline but not of glucagon, have adduced experimental evidence to indicate that the hyperglycemic factor found in the pancreaticoduodenal vein of growth hormone treated animals(3,4) is an adrenaline-like substance. Osman Saka(5), while working on the hyperglycemic glycogenolytic factor of the pancreas, found that 4 ml of blood from an alloxan diabetic rabbit, when injected to a normal rabbit elicited a hyperglycemic response. This hyperglycemic response was attributed to the presence of glucagon in the blood of alloxan diabetic rabbits. In view of the observations of Sirek *et al*, it was thought desirable to determine whether the hyperglycemic factor, reported by Saka was an adrenergic substance.

Acetoacetate has been reported to cause hyperglycemia and associated disturbances in carbohydrate metabolism(6,7). Repeated daily injections of acetoacetate to normal and scorbutic guineapigs were found to increase the adrenaline content of the adrenals(8). Therefore, it was decided to investigate the possible presence and nature of a hyperglycemic substance in the blood of acetoacetate treated animals. Experiments were also performed to determine whether adre-

nergic mediation played a part in the immediate hyperglycemia following a single injection of acetoacetate to rabbits.

*Materials and methods.* Rabbits were made diabetic by intravenous injection of alloxan. Eight of these rabbits, having blood sugar values above 200 mg % a week after the alloxan injection, were used as blood donors.

Eight rabbits were injected with sodium acetoacetate, intraperitoneally every day for 2 months. The starting dose of acetoacetate was 100 mg/kg and it was increased by 50 mg/kg every 15 days. At the end of 2 months, those rabbits which had blood glucose values of about 170 mg % were used as blood donors, to test the presence of an adrenergic substance in their blood.

Four ml of blood from each of 8 alloxan diabetic rabbits along with 10 mg heparin was injected in the marginal ear vein of normal rabbits. The blood sugar of the recipient rabbits was determined by Nelson's method(9) every 10 minutes. Four ml of blood from the alloxan diabetic rabbits was similarly injected to other normal rabbits, which had been injected with dihydroergotamine (0.2 mg/kg) half an hour earlier, and the blood glucose content of the recipients determined every 10 minutes. The results are presented in Fig. 1.

Ten to sixteen mg of glucose (which was the amount present in 4 ml of alloxan diabetic blood injected to normal rabbits) along with 10 mg heparin was added to 4 ml of

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