the two diuretics used.

Discussion. A higher incidence of delayed deaths occurred from the administration of Mercurophylline to which Sodium Thioglycollate had been added. This substantiated preliminary testing in which it was found that 0.1 cc of Sodium Thioglycollate and 0.1 cc of Mercurophylline (4.0 mg of mercury) when mixed and injected subcutaneously had a greater toxicity than either drug administered alone. Control injections of 30 mg of Sodium Thioglycollate subcutaneously were non-toxic. The toxicity of the combined Mercurophylline and Sodium Thioglycollate following subcutaneous administration is approximately double that of Mercurophylline and is even greater than that of Mercurophylline with benzyl alcohol when given by this route. The toxicity of this combination of mercurial and thiol is, however, of the same order as that of Thiomerin given subcutaneously in rats, a fact which might be anticipated from their similarity of chemical composition. Thus, the addition of the thiol compound, even though it eliminates the danger of acute death following intravenous injection, so increases the chronic toxicity of Mercurophylline by either subcutaneous or intravenous routes that its addition would seem to be a decided hazard.

Summary. Data presented on the comparative toxicity of Thiomerin, Mercuhydrin and Mercurophylline indicate that the compound containing the thiol group definitely is more toxic in rats. Other reports, both clinical and laboratory, have indicated such a possibility. Sodium Thioglycollate potentiates the chronic toxicity of Mercurophylline when combined with it and given by either the subcutaneous or intravenous route. There is, however, elimination of the acute cardiac effect with intravenous administration. Studies of the distribution of mercury in the rat and its excreta following subcutaneous administration of two of the drugs failed to indicate the mechanism of potentiation of toxicity.

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Pancreatic Secretion to Peptic Ulcer. II. Effect of Hypoglycemia With and Without Pancreatectomy.* (17957)

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A definite relationship exists between pancreatic function and peptic ulcer formation. When the alkaline pancreatic secretions are deviated from the duodenum by external pancreatic fistula, ligation of the pancreatic ducts or by implantation of the ducts into the lower reaches of the gut without ablation of the pancreas, peptic ulcers develop spontaneously (1-4). However, if the duodenum is deprived of the alkaline external secretinos by means of pancreatectomy, ulcers form spontaneously only rarely. It was suggested by Poth, Manhoff, and DeLoach(5) that this difference might be due to the fact that the hyperglycemia due to pancreatectomy suppresses secretion of the gastric acid-pepsin factor sufficiently to protect the gastric and duodenal mucosa from ulceration. The experiments reported in this paper are directed toward the evaluation of this assumption.

Experimental method. Twenty healthy, mongrel dogs were divided into 2 equal groups. Their food consisted of 50 g of raw

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TABLE I.
Sample Protocol (Dog No. 9) Showing Insulin Dosage and the Resulting Blood Sugar Levels.

Date	Blood sugar mg % 8 a.m.	12 n.	4 p.m.	PZI insulin units	Remarks
9/14	55			0	Pancreatectomy (normal blood sugar level before pancreatectomy varied between 56 and 69 mg %)
15	362			3	
16	200			3	
17	132			3	
18	241			0	
19	241			4	
20	44	62	129	4	
21	27	45	239	4	
22	29	32	63	4	
23	20	30	30	4	
24	22			4	
25	23			0	Clinically hypoglycemic
26	244	266	332	4	
27	34	53	123	4	
28	16	54	46	4	
29	38	100	139	4	
30	34	39	66	4	
10/1	17			4	
2					Dead. Autopsy. Several small gastric ulcers

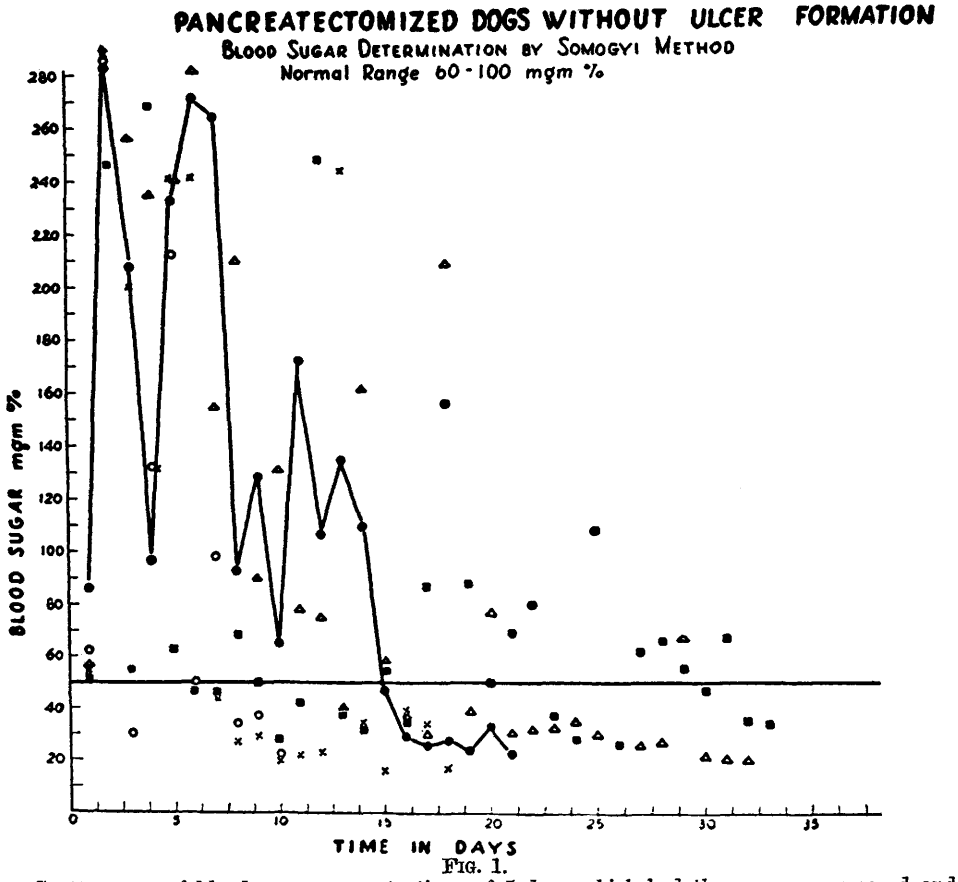

FIG. 1.

Scattergram of blood sugar concentrations of 5 dogs which had the pancreas removed and were then administered commercial protamine zinc insulin in sufficient quantity to reduce the blood sugar level below 50 mg % and eventually result in the animal's death. A curve is drawn through one set of points. There were no peptic ulcers present when these animals died.

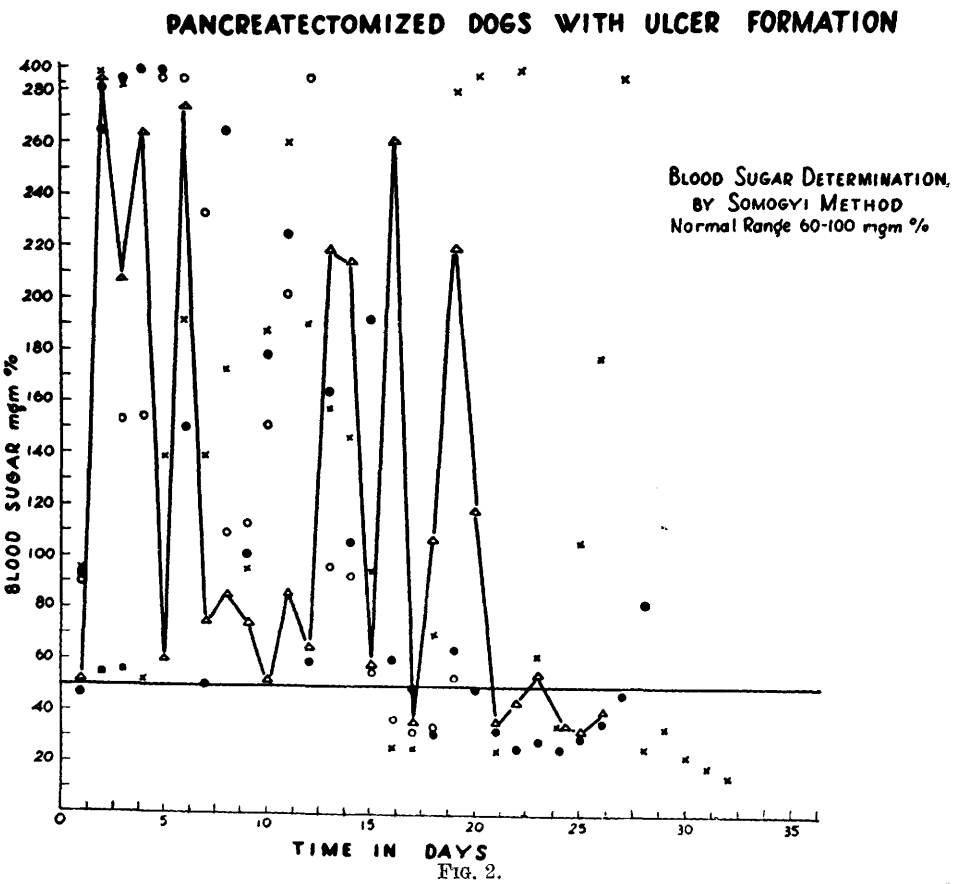

FIG. 2.

Scattergram of blood sugar concentrations of 5 dogs which had the pancreas removed and were then administered commercial protamine zinc insulin in sufficient quantity to reduce the blood sugar level below 50 mg % and eventually result in the animal's death. A curve is drawn through one set of points. Each of these animals developed peptic ulcers.

horse meat daily per kilo of body weight. Initial daily fasting blood sugar levels were obtained during a control period of a few days. One group was then treated with commercial protamine zinc insulin to lower the fasting blood sugar level to 50 mg % or less. The other group was first subjected to pancreatectomy and one gram of choline was added to their daily diets to protect against fatty changes in the liver. Three units of protamine zinc insulin were given daily for five to seven days immediately postoperatively to maintain approximately normal blood sugar levels. Then the dosage of insulin was gradually increased until the fasting blood sugar level was maintained below 50 mg %; preferably in the neighborhood of 40 mg %, Table I. It was difficult to maintain these conditions because an animal might fail to eat all of his food, and also because the animals developed a certain degree of tolerance to insulin. This latter phenomenon was noticed particularly in the animals which had not been pancreatectomized. The administration of insulin was continued until the animals expired. Death frequently resulted from hypoglycemic shock and convulsions. To demonstrate that the changes observed were not due to the convulsions, *per se*, 3 animals were administered metrazol and maintained in a continuous convulsive state for one to three hours. Autopsy performed immediately following the death of these control animals showed the mucosa of the gastrointestinal tract to be normal except for an occasional small, petechial, submucosal hemorrhage. Ulceration had not occurred.

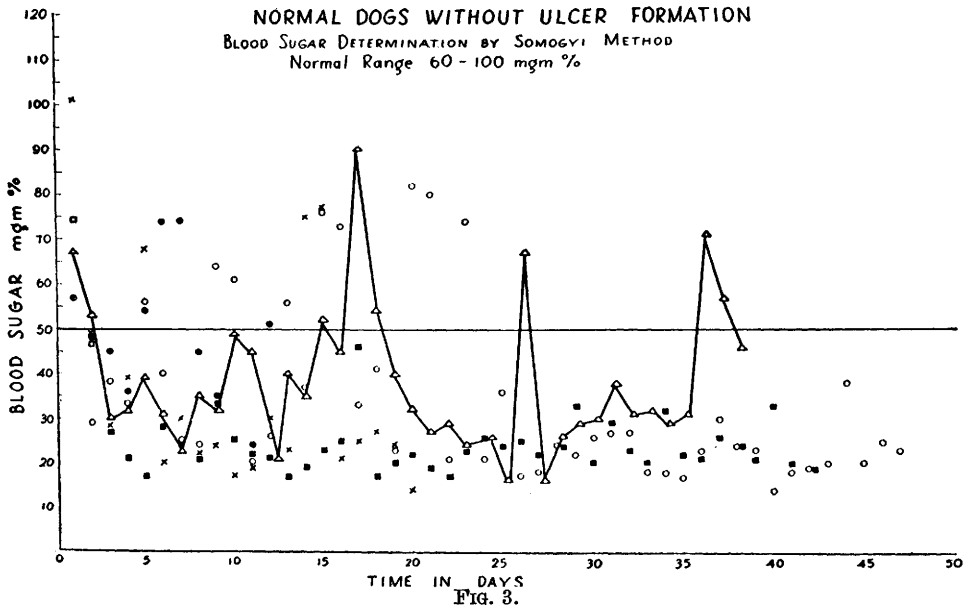

FIG. 3.

Scattergram of blood sugar concentrations of 5 normal dogs which had received commercial protamine zinc insulin in sufficient quantity to reduce the blood sugar level below 50 mg % and eventually result in the animal's death. A curve is drawn through one set of points. There were no peptic ulcers present when these animals died.

Therefore, it is believed that the postmortem ulcers found in the hypoglycemic animals were not due to terminal convulsions.

All animals were examined postmortem for the presence or absence of gastrointestinal ulceration. No residual pancreas could be found in the pancreatectomized animals. The specific data of these experiments are presented in Fig. 1, 2, 3, and 4.

Comparison of the blood sugar levels of the depancreatized animals given in Fig. 1, which failed to form ulcers, with those of Fig. 2, which developed ulcers, shows no appreciable difference in the degree of hypoglycemia. Likewise, the comparison of these data given in Fig. 3 and 4 from similar studies on intact dogs again fails to show any significant difference of blood sugar levels whether or not ulcers developed. Probably all of the animals developed ulcers, but, since they heal so rapidly, they may not be present at time of the animal's death which results from the hypoglycemia.

Discussion. Maintenance of hypoglycemia is rather difficult because of individual variation of susceptibility and because a degree of tolerance to insulin develops. Apparently, the ulceration begins with disruption of the surface cells of the mucosa. This superficial damage is rapidly repaired when the blood sugar level is allowed to return to, or exceed, normal values. Completely reproducible conditions cannot be maintained and might account for the fact that demonstrable ulcers are not produced in all experiments. The incidence of ulcer formation is such, however, as to indicate that hypoglycemia favors the development of peptic ulcers both in the intact animal and in those subjected to pancreatectomy. Peptic ulcers were found at autopsy in half of the animals of both groups.

If hypoglycemia will favor the development of peptic ulcers, then individuals with islet cell tumors of the pancreas showing sustained hypoglycemia should have a high incidence of peptic ulceration. Only a single instance of peptic ulcer accompanying islet cell tumor is found on careful search of the literature. Can one explain this apparent paradox? Commercial insulin is not pure. It may contain as much as 10% of a substance called the H-G factor. This factor causes hyperglycemia and can hydrolyze glycogen. This H-G factor has been isolated from the mucosa

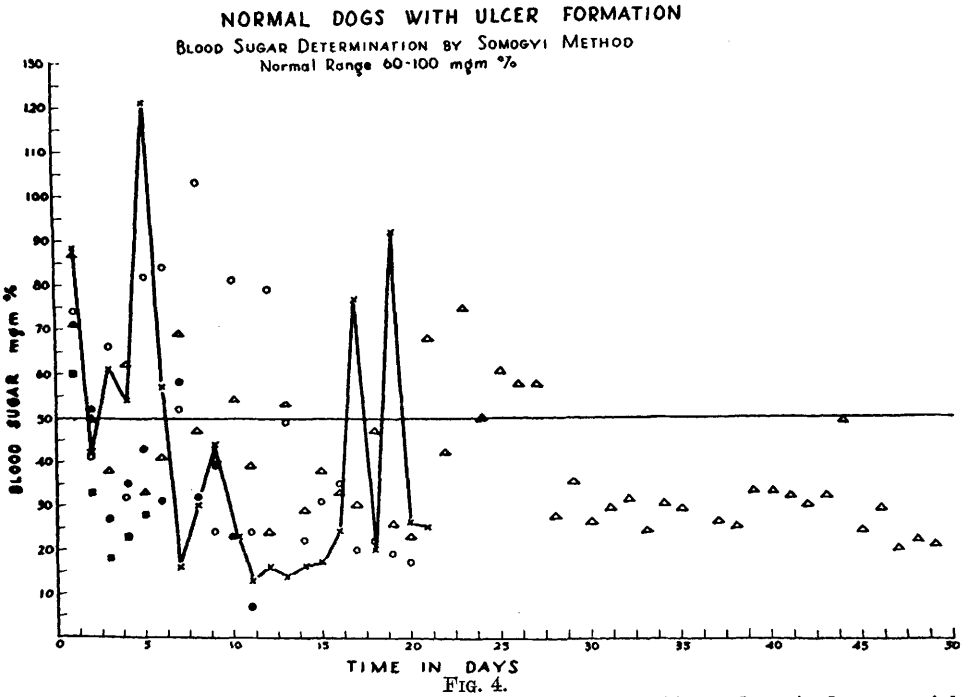

FIG. 4.

Scattergram of blood sugar concentrations of 5 normal dogs which had received commercial protamine zinc insulin in sufficient quantity to reduce the blood sugar level below 50 mg % and eventually result in the animal's death. A curve is drawn through one set of points. Each of these animals developed peptic ulcers.

of the stomach and duodenum(6). This factor is believed to be formed by the alpha cells of the islets of the pancreas while insulin is produced by the beta cells. Islet cell adenomata consist largely of beta cells. Can it be that insulin free of the H-G factor will fail to favor the formation of ulcers? This question is being studied by repeating the above work using purified insulin. Is the H-G factor responsible for peptic ulceration through its glycogenolytic property, or is ulceration due primarily to increased gastric activity induced by hypoglycemia?

Summary. 1. Dogs were maintained in a state of hypoglycemia by the administration of insulin. 2. These animals were divided into 2 equal groups. The animals of one group were pancreatectomized. 3. Half the animals of each group developed ulcers. 4. The absence of peptic ulcer formation in patients suffering from islet cell tumors and hypoglycemia is discussed.

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