also the intracellular ones, aside from the enzymatic functions of the latter. Moreover, the degree to which the microorganisms of the gastro-intestinal tract are responsible for the experimental findings has not been evaluated. The parenteral administration of the malonate should reduce the importance of this factor but does not necessarily eliminate it.

Summary. When C^{13} - carboxyl - labeled malonate was injected subcutaneously into mice, 20-32% of the labeled carbon was recovered in the respiratory carbon dioxide in 6 hours.

At body temperature, dog plasma showed little or no ability to decarboxylate malonate.

These results are interpreted to indicate the probable occurrence in mammalian cells of enzymatic mechanisms for conversion of malonate to carbon dioxide.

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Antibiotics in the Treatment of Experimental Acute Hemorrhagic Pancreatitis in Dogs. (17937)

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In a study on the pathogenesis of acute pancreatitis Dragstedt, Haymond, and Ellis (1) reported that devitalized dog pancreas, highly toxic when allowed to autolyze within the peritoneal cavity, was not toxic after being sterilized in the autoclave. Also, sterile fetal pancreas was not toxic when placed within the dogs' peritoneal cavity. Within the uncontaminated pancreas of 13 out of 17 dogs, bacteria common to the intestinal tract were found. *B. welchii* was especially common. No matter what the cause of the necrosis in acute pancreatitis might be, these authors felt that the resulting toxemia was the same and in the major part believed that it was due to the bacterial decomposition products of proteins. These observations suggested to us that antibiotics might be of value in treating experimental pancreatitis in dogs.

Methods. Healthy, adult, dewormed, mongrel dogs were used. Pancreatitis was produced aseptically in the same manner in all the dogs by injecting the animal's own gallbladder bile into its major pancreatic duct and then tying the duct. To produce an hemorrhagic, necrotic pancreatitis with a high fatality rate in non-treated animals it was found necessary to inject a relatively large amount of bile under pressures much higher than have been found normally in the biliary tract of the dog(2). An average of 10.5 cc of bile were injected into the main pancreatic duct extraduodenally through a 20-gauge needle within less than one minute. Pressure readings taken with a mercury manometer attached to a side arm showed pressures of 400 to 500 mm of mercury during the injection. After a satisfactory injection, the pancreatic parenchyma would be stained diffusely; often there would be a mottled brown appearance as described by Mann and Giordano(2).

The animals treated with penicillin were given 300,000 units of penicillin G in 1 cc of oil and wax* intramuscularly, beginning within 4 hours after surgery and continuing once daily for 4 or 5 days. Streptomycin hydrochloride* was given subcutaneously in doses of 0.17 g beginning within 4 hours after the pancreas was injected and continuing every 4 hours, except for the 4:00 A.M. dosage, for

1. Dragstedt, L. R., Haymond, H. E., and Ellis, J. C., *Arch. Surg.*, 1934, v28, 232.

2. Mann, F. C., and Giordano, A. S., *Arch. Surg.*, 1923, v6, 1.

* Provided by E. R. Squibb and Sons, New York City.

TABLE I.
Survival of Dogs with Experimental Pancreatitis.

Type	No. of dogs	Survivors	Deaths
1. Penicillin treatment postoperatively	31*	18	13 (42%)
2. Streptomycin treatment postoperatively	6	3	3
3. Penicillin and streptomycin treatment postoperatively	5	3	2
4. Intestinal "sterilization" preoperatively with streptomycin, sulfasuxidine, or both	10	3	7
5. Pancreatectomy after development of pancreatitis	7	1	6
6. Controls	23†	5	18 (78%)

* 9 had 100,000 units of penicillin intraperitoneally at the time pancreatitis was produced and 6 of these had one injection of penicillin preoperatively. Five others were explored during the first few days postoperatively.

† 2 dogs were explored in the immediate postoperative period.

4 or 5 days. The animals given sulfasuxidine, streptomycin or both preoperatively in order to reduce the intestinal flora received 3 g of sulfasuxidine orally twice a day or 0.5 g of streptomycin orally twice a day for 4 to 5 days before pancreatitis was produced. When a total pancreatectomy was used as a method of treatment it was done aseptically through the old incision under sodium pentobarbital anesthesia within 30 hours following production of the pancreatitis.

Experiments and results. Results in the 6 series of animals used are summarized in Table I. The animals that died of acute pancreatitis succumbed within 4 days postoperatively and usually within the first 48 hours. At autopsy there was a generalized peritonitis with extensive fat necrosis in the upper abdomen and marked swelling of the pancreas with hemorrhagic areas and occasional frank necrosis. When autopsied the survivors usually had a shrunken cord-like pancreas with some nearby adhesions but no other abnormalities.

Those treated with penicillin in Series I had a significantly higher survival rate than the control animals which were treated the same way except for the penicillin. Using a modification of the χ^2 test for 4-fold tables (3) the probability of the differences noted arising through the errors of random sampling is .008. If the animals given penicillin preoperatively and intraperitoneally as well as those explored postoperatively are omitted from consideration, the difference between the fatality rates among those treated with penicillin postoperatively and the controls is still significant with a $P = .029$. The animals treated with streptomycin or a combination of penicillin and streptomycin also seemed to have a higher survival rate than the controls but the series are probably too small to be significant. Attempts to reduce the bacterial flora of the intestinal tract before producing pancreatitis as well as a total pancreatectomy after the development of pancreatitis failed to reduce the fatality rate below that noted in the controls.

Discussion. The effectiveness of parenteral penicillin treatment in reducing the mortality of experimental pancreatitis supports the conclusion of Dragstedt, Haymond, and Ellis(1) that bacteria normally resident in the dog pancreas are important in developing the toxemia of pancreatic necrosis. Similarly the value of penicillin in treating the toxemia following complete hepatic artery ligation(4) or following the intraperitoneal autolysis of detached segments of canine liver(5) has favored the theory that bacteria normally

3. Treloar, Alan E., Elements of Statistical Reasoning, John Wiley and Sons, New York, 1939.

4. Markowitz, J., Rappaport, A., and Scott, A. C., PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 305.

present in the dog liver are important in producing the fatal toxemia of liver autolysis(6).

If it is assumed that the bacteria normally present in the dog pancreas arise from the intestine, reduction of the intestinal bacterial count following oral streptomycin or sulfasuxidine should in time reduce the number of pancreatic bacteria. Effective pancreatic sterilization should then reduce the toxicity of experimental pancreatitis. The failure of these methods to reduce the mortality may be due to an inadequate pancreatic sterilization, for the two animals in the group in which pancreatic cultures were taken before pancreatitis was produced both had gram positive bacteria in the pancreas.

We have no evidence that antibiotics are effective in treating acute hemorrhagic pancreatitis in humans.

Conclusions. 1. Treatment with penicillin G in oil and wax has been effective in lowering the fatality rate of experimental hemorrhagic pancreatitis in dogs. 2. Total pancreatectomy as a treatment or preoperative oral streptomycin or sulfasuxidine as prophylaxis have been ineffective.

5. Lewis, F. J., and Wangensteen, O. H., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 533.

6. Ellis, J. C., and Dragstedt, L. R., *Arch. Surg.*, 1930, v20, 8.

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Pituitary Basophile Hyperplasia and Crooke's Hyaline Changes in Man After ACTH Therapy. (17938)

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(Introduced by P. B. Beeson)

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A significant increase in the basophilic cells associated with Crooke's hyaline cytoplasmic changes was found in the anterior pituitary of two patients following adrenocorticotropic hormone therapy. To our knowledge these findings have not previously been reported in man.

Material. The first patient was a 43-year-old white man with chronic glomerulonephritis who was given a course of ACTH therapy. He died in uremia on the fifth day of treatment having received a total dose of 400 mg intramuscularly. Autopsy confirmed the diagnosis of chronic glomerulonephritis. The combined weight of the adrenal glands was 18.5 g. Histologic examination of the pituitary suggested a distinct increase in basophilic cells, which displayed striking hyaline cytoplasmic changes as described by Crooke in Cushing's syndrome(1). Many of the chromophobe cells showed definite basophilic stippling, suggesting a transition between these and the basophilic cells. Both chromophobes and basophiles were most prominent in the anterior portion of the lobe. No increase in basophiles was noted in the pars intermedia and there was no basophilic infiltration of the posterior lobe.

The second patient was a 19-year-old white nullipara with chronic glomerulonephritis who received 490 mg of ACTH intramuscularly over a period of 8 days, terminating 7 days prior to death in uremia. Autopsy showed chronic glomerulonephritis. The combined weight of the adrenal glands was 18.5 g. Gross examination of the pituitary gland revealed a speckled yellowish gray appearance of the anterior lobe.

Histologic examination suggested a diffuse increase in basophilic cells with a concentration in the anterior and central portions. A minimal basophile infiltration of the posterior lobe was noted. Hyaline cytoplasmic changes of the basophiles were present in only a few scattered cells. Many chromophobes in both

1. Crooke, A. C., *J. Path. and Bact.*, 1935, v41, 339.