It was found that there was a progressive elevation of the threshold of the vomiting mechanism to digitalis. Thus the initial dose of the drug which induced vomiting, when repeated often failed to produce this result, and increasingly larger doses were required to cause vomiting. It was found that the cumulation of digitalis after repeated injections might produce very severe poisoning of the heart as indicated by the development of such toxic rhythms as ventricular tachycardia, while at the same time vomiting did not occur. In fact, in 3 dogs the final increment of digitalis which was fatal failed to cause vomiting, though sufficient time elapsed before death for vomiting to have occurred.

The above facts are illustrated by Fig. 1, which shows selected electrocardiograms from one of the shorter experiments. It may be seen that digitalis given by vein produced vomiting in 4 minutes (tracing 3), and that subsequently an intravenous injection of oubain was followed by vomiting in 8 minutes (tracing 11). On the following day, however, the same intravenous dose of oubain induced a toxic rhythm resulting in death, but failed to cause emesis although 17 minutes had elapsed before the animal died (tracings 23, 24, 25).

Because of the significance attached to the symptom of vomiting as an index of toxicity in digitalis therapy, the possibility of depression of the vomiting mechanism to digitalis apparent in these experiments must be taken into consideration in the clinical use of the drug.

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Liver Changes After Deprivation of External Pancreatic Secretion.

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In a recent investigation concerning the physiology of pancreatic secretion[1] a series of dogs was deprived completely of pancreatic juice by means of fistulas made according to the Elman and McCaughan modification of the Rous-McMaster technique[2] and by

[1] Berg, B. N., and Zucker, T. F., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 724. Zucker, T. F., Newburger, M. G., and Berg, B. N., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 666.

[2] Elman, R., and McCaughan, J. M., *J. Exp. Med.*, 1927, **45**, 561.

ligation of the pancreatic ducts. At autopsy, histological examination of the livers of these animals revealed striking changes. In fistula dogs which succumbed 7 to 10 days after the loss of pancreatic juice, early degenerative changes such as cloudy swelling and moderate fatty infiltration of the liver cells were observed. In fistula dogs which survived for longer periods (17, 20, 20, 20, 24, 25, 25, 32, 51 and 56 days respectively) the histological alterations were more pronounced and consisted of one or more of the following: fatty infiltration and necrosis of the liver cells, congestion of the capillaries around the central veins, atrophy of the liver cords, dilatation of the bile canaliculi and biliary cirrhosis. Some of the animals in this group received daily intravenous injections of NaCl and $NaHCO_3$; others continued for 3 weeks or longer without any form of treatment. Extensive fatty infiltration of the liver also occurred after prolonged obstruction of the pancreatic ducts (80 days).

After varying periods of exclusion of pancreatic secretion from the intestine, the dogs lost their appetites, declined rapidly in weight, showed marked weakness and apathy, became jaundiced in a few instances, developed a bloody diarrhea and finally succumbed. Vomiting did not occur except in isolated instances.

Allan, Bowie, MacLeod and Robinson[3] observed similar symptoms and pathologic changes, in depancreatized dogs treated with insulin. They found an actual increase in the total lipids of the liver and suggested that the pancreas produced an internal secretion, possibly a lipase, which was required by the liver for the mobilization of fat. Fisher[4] noted that the livers of depancreatized dogs kept alive with insulin were fatty. Pflüger[5] had found that the fat content of the livers of dogs was greatly increased after subtotal pancreatectomy and ligation of the pancreatic ducts. Microscopic examination revealed fatty infiltration of the liver cells in the periphery of the lobules and an accumulation of brown pigment in the cells in the central areas. Lombroso[6] concluded from his experiments that the pancreas contained an internal as well as an external secretion which played a rôle in the assimilation of fat. Lombroso also noted that dogs with pancreatic fistulas made according to Pawlow's technique

[3] Allan, F. N., Bowie, D. J., MacLeod, J. J. R., and Robinson, W. L., *Brit. J. Exp. Path.*, 1924, **5**, 75.

[4] Fisher, N. F., *Am. J. Physiol.*, 1924, **67**, 634.

[5] Pflüger, E., *Arch. f. d. ges. Physiol.*, 1905, **108**, 115.

[6] Lombroso, U., *Arch. f. d. ges. Physiol.*, 1906, **112**, 531; *Arch. f. exp. Path. u. Pharm.*, 1908, **60**, 99.

never survived longer than 3 months if the minor duct was ligated at the time of the establishment of the fistula. In addition he observed that many animals began to show signs of extreme weakness and marasmus 30 to 40 days after ligation of both pancreatic ducts and died shortly afterward. He was unable to explain the cause of death of these animals. Recently Hershey and Soskin,[7] continuing the work of Allan, Bowie, MacLeod and Robinson came to the conclusion that the liver was the seat of the major disturbances following pancreatectomy in dogs and that the symptoms were attributable to "liver failure". They believed that the disturbance in the liver was concerned principally with faulty fat metabolism. The addition of "lecithin" to the diets of their animals alleviated the symptoms and improved the function of the liver.

Since our studies show that the symptoms and liver changes following the drainage of pancreatic juice by a fistula or after ligation of the pancreatic ducts are practically identical with those following pancreatectomy, it seems likely that the underlying factor common to the 3 conditions is the absence of the external secretion from the intestine. Our observations indicate that the pancreatic juice contains a substance, possibly hormonal in nature, which is reabsorbed from the intestinal tract and is concerned with fat metabolism in the liver. The marked fatty infiltration which occurs in the liver[8] after the diversion of the portal blood by an Eck fistula may also be associated with a prolonged deficiency in this factor. The liver changes which are found after prolonged inanition resemble those which develop after the deprivation of pancreatic juice. We are undoubtedly dealing with a rather complex phenomenon and at this time merely wish to report our findings to date. It is apparent that a deficit of electrolytes[9] is by no means the only untoward result following the drainage of pancreatic secretion through a fistula.

[7] Hershey, J. M., and Soskin, S., *Am. J. Physiol.*, 1931, **98**, 74.

[8] Berg, B. N., Cone, W. V., and Jobling, J. W., PROC. SOC. EXP. BIOL. AND MED., 1925, **23**, 81.

[9] Gamble, J. L., and McIver, M. A., *J. Exp. Med.*, 1928, **48**, 859.