Peptic Ulcer Following Portacaval Shunt *

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1. Clinical Observations

EVERY PATIENT with cirrhosis of the liver and massive upper gastro-intestinal hemorrhage presents a diagnostic problem. Is he bleeding from gastroesophageal varices or from benign peptic ulcerations? The problem is aggravated by the frequent coexistence of varices and ulcer. Numerous autopsy and clinical studies in recent years have focused on this association and have shown that it is more common than expected by chance.

Fainer and Halsted [13] reviewed 1,278 consecutive autopsies and found Laennec's cirrhosis present in 94 cases or 7.4 per cent. Peptic ulcer was present in 17 per cent of these 94 cases of cirrhosis, and in 10.6 per cent of the other 1,184 cases which had no cirrhosis. They also studied 200 cases with a clinical diagnosis of Laennec's cirrhosis of which 76 bled from the upper alimentary tract. Peptic ulcer was proved to be responsible for the bleeding in 18.4 per cent, gastric erosion in 5.3 per cent, and esophageal or gastric varices in 61.8 per cent. Davis [9] found eight chronic peptic ulcers and six acute peptic ulcers in 100 consecutive autopsied cases of cirrhosis. Schnitker and Hass [24] found ulcers in 19.5 per cent of 72 patients with cirrhosis. Swisher, Baker, and Bennett [26] studied 417 cases of Laennec's cirrhosis and found peptic ulcer in 13.9 per cent. Reports on the incidence of peptic ulcer with cirrhosis have been summarized by Koide, Texter, and Borden,[19] and incidence varies from 3.6 per cent up to 24.7 per cent. The evidence from autopsy studies cited above is convincing, while that from the clinical studies suffers from lack of comparable control groups. Still the incidence of peptic ulcer in patients with cirrhosis is undoubtedly high and the correlation probably denotes some underlying casual relation.

Portavacal shunting procedures were introduced in 1945 by Blakemore, Whipple and co-workers.[4, 27] With increased numbers of cases and the passage of time new questions concerning their effects are gaining general interest. One of these centers on the ulcer problem. Does successful portacaval shunt reduce, augment, or have no influence on the ulcer tendency found in patients with hepatic cirrhosis?

Dubuque, Mulligan, and Neville [12] observed 60 patients up to eight years after end-to-side portacaval anastomosis. Upper gastro-intestinal ulceration developed in 15 per cent. Aside from this report we have found only sporadic references in the literature to upper alimentary tract ulcers developing after portacaval shunt. Hallenback and Shocket [17] had 17 patients who survived splenorenal shunt and 23 patients who survived end-to-side portacaval shunt. Subsequent bleeding from a co-existing duodenal ulcer was diagnosed in two of the latter 23 patients, the evidence being clin-

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ical in one and postmortem in the other. The autopsied patient had a known duodenal ulcer which had bled 16 years before shunt. Blakemore [3] reported a one month to seven year follow up on 130 patients who survived splenorenal or portacaval shunt. Two of these patients, each of whom had a splenorenal shunt for intrahepatic disease, died with gastric ulcers. Child [6] noted one patient with active duodenal ulcer two years after portacaval shunt out of 27 patients who survived portacaval shunt and four who survived splenorenal shunt. McDermott [22] described an interesting case of a man who had a portacaval shunt for portal cirrhosis and developed upper gastro-intestinal distress and heartburn three months later. The patient then bled and died in coma. At autopsy he had a 4.0 cm. duodenal ulcer in the second portion of the duodenum. On the other hand in some sizable series of portacaval and splenorenal shunts no subsequent gastroduodenal ulcers have been reported.[18, 21, 23]

From a total number of 62 portacaval shunts done in three Southern California hospitals we have collected a group of four patients who developed ulcers within a year after shunts. A fifth patient had worsening of a pre-existing ulcer after shunt. Twenty-nine of these shunts were done at the Veterans Administration Center, Los Angeles, 17 at the Veterans Administration Hospital, Long Beach, and 16 at the University of California Medical Center, Los Angeles. The earliest was done in 1948, the most recent in June 1957. Brief summaries of these five cases follow.

Case Reports

Case 1. O. W. B. was a 56-year-old brewery worker who was first seen in 1950, with weight loss, weakness, jaundice, moderate ascites, marked impairment of liver function tests, and a history of drinking about seven beers daily for six years. There was no history of ulcers or bleeding. Gastroduodenal x-rays on March 6, 1951 did not demonstrate varices or ulcers. He did well on medical management for six months, but then hematemesis occurred which was controlled by balloon tamponade. Liver punch biopsy showed active portal cirrhosis. On March 30, 1951 end-to-side portacaval shunt was performed with a fall in portal pressure from 30 to 12 cm. of saline.

Three months after shunt he again had hematemesis. The bleeding stopped with ulcer therapy and transfusions. Nine months after shunt he developed epigastric ulcer type pain. X-ray on December 14, 1951 showed a 1.5 cm. lesser curvature gastric ulcer. The ulcer persisted despite medical treatment and on April 17, 1952 a wedge resection of the lesser curvature of the stomach was done, removing an active ulcer 2.0 cm. in diameter. Subsequently there was persistent bloating and epigastric distress. X-ray on January 23, 1953 showed marked retention and a huge recurrent gastric ulcer, and a Billroth I type of subtotal gastric resection was done on February 16, 1953. After this operation the patient was free of bleeding and ulcer pain. He began to drink heavily 18 months later and died at home on March 31, 1955. No autopsy was done but the death certificate said he died of cirrhosis of the liver.

Case 2. C. R. W. was a 54-year-old male, an alcoholic for 21 years who was first seen on January 13, 1953 with massive hematemesis. X-rays showed esophageal varices but no ulcers. Liver punch biopsy revealed cirrhosis. On April 21, 1953 an end-to-side portacaval shunt was done with a fall in portal pressure from 39 to 20 cm. of saline. Three months after shunt he returned with hematemesis and melena. An ulcer crater on the superior margin of the prepyloric area of the stomach was found by x-ray and gastroscopy. There was no ulcer type pain associated with this bleeding and there was no history of previous ulcers. Transfusions were given, strict medical treatment begun, and the prepyloric ulcer disappeared. Six months after shunt the patient developed ulcer type pain. X-rays on October 20, 1953 showed an ulcer in the posterior portion of the duodenal cap, while the esophageal varices had disappeared. Because the patient refused operation he was continued on medical management.

One year after shunt he was re-admitted with melena of 9 hours' duration and ulcer pain for the past month. He became stuporous and febrile, and developed pneumonia. Despite transfusions and antibiotic therapy he died on April 24, 1954. At autopsy there was severe Laennec's cirrhosis, an open portacaval anastomosis, and suppurative bronchopneumonia. An ulcer on the posterior wall of

the duodenal bulb, 7 mm. in diameter and penetrating deep through the mucosa, appeared to be the source of bleeding.

Case 3. G. E. F. was a 39-year-old clerk who had jaundice in Africa in 1943, probably due to infectious hepatitits. In August 1955, he had hematemesis and melena, and was admitted to the Veterans Administration Hospital, Long Beach. He rarely drank alcoholic beverages. On admission he had an enlarged liver and spleen, palmar erythema, spider angiomata, persistent leukopenia and thrombocytopenia, and moderately impaired liver function tests. X-ray on September 22, 1955 revealed large esophageal varices and a normal duodenal bulb. On November 9, 1955 an end-to-side portacaval shunt was done, portal pressure falling from 42 to 24 cm. of saline. Liver biopsy at this operation showed active portal cirrhosis. Recovery was uncomplicated. The spleen diminished in size, the leukopenia subsided, and x-ray on December 9, 1955 showed only minimal esophageal varices.

During the next 15 months the patient had numerous admissions for three major complaints. With any increased activity he noted weakness and ankle swelling. Despite good treatment his liver function tests remained abnormal, and smoldering viral hepatitis was diagnosed. Beginning 9 months after shunt he developed right upper quadrant pain which was at first intermittent but later persistent and severe. At various times it involved the right lower anterior chest, the right back and lumbar areas, and both subscapular regions. It was usually dull and aching in nature, was relieved by moving about, but not helped by 0.030 Gm. of codeine. There was hyperesthesia over the operative scar, which was tender, and the pain was allayed for 4 hours by procaine block. In addition, the patient had tarry stools for three days in October 1956. X-rays on October 2, 1956 showed a normal esophagus without varices, and no gastric or duodenal lesions were seen. On February 27, 1957 hematemesis occurred, coma developed, and the patient died March 1, 1957.

At autopsy the portacaval shunt was open, there was active hepatitis and extensive cirrhosis, and the esophageal veins were only slightly prominent. The stomach and small bowel were filled with blood. A huge ulcer, 6.0 cm. long, 3.0 cm. wide, and 1–2 cm. deep, lay just at the pylorus, and was penetrating posteriorly into the pancreas.

Case 4. R. H. was a 49-year-old man who had been a heavy drinker for 10 years until attacks of hematemesis and melena in May and October 1955, requiring multiple transfusions and use of esophageal tamponade. He had never had symptoms suggestive of ulcer. He was admitted to the U.C.L.A. Medical Center on December 15, 1955 where he was found to have an enlarged liver and spleen, no ascites, prothrombin time of 50 per cent, 3 plus cephalin flocculation test, and normal plasma proteins and serum bilirubin. A recent x-ray disclosed esophageal varices and no sign of duodenal ulcer. On December 20, 1955 a splenectomy and side-to-side portacaval shunt were performed for Laennec's cirrhosis with esophageal varices. Portal pressure fell from 46 to 24 cm. of saline. Recovery was smooth.

Two months after shunt the patient experienced gas, belching and the onset of right upper quadrant pain which came on three hours after meals and was relieved by food or antacids. X-rays on April 26, 1957 demonstrated improvement in the esophageal varices; no ulcer was seen, but the amount of nonopaque fluid in the stomach and prolapse of the pyloric mucosa were interpreted as consistent with gastritis and moderate hypersecretion. On antacid therapy the symptoms disappeared in four days. The patient did not continue his ulcer management.

Six months after shunt the patient was readmitted because of weakness, passage of a tarry stool, and a hematocrit of 24 per cent. The stools became free of blood after three days of ulcer treatment. X-rays on June 24, 1957 revealed pylorospasm, an irritable duodenal bulb, and a small ulcer in the pyloric canal. There was a suggestion of remaining esophageal varices. On hourly antacids, phenobarbital, and bed rest the patient did well. He was discharged and has since remained on ulcer treatment and free of symptoms.

Case 5. E. W. H. was a 67-year-old machinist who was admitted to the Veterans Administration Hospital, Long Beach, on January 1, 1957 during his third episode of hematemesis and melena in two months. Three months perviously he had developed ascites and x-ray had shown esophageal varices. There was no history of hepatitis, exposure to hepatotoxins, or excessive alcoholic intake. Two years previously he had epigastric pain, a scarred duodenal bulb was seen by x-ray, and alkalis relieved the distress.

On admission there was ascites and the liver was enlarged. Liver function tests were moderately impaired. X-rays showed esophageal varices. Although there was marked spasm and irritability of the duodenal bulb, compatible with ulcer, no crater was seen. On January 21, 1957 end-to-side portacaval shunt was done, portal pressure falling from 31 to 18 cm. of saline. Liver biopsy at this time revealed active portal cirrhosis. Convalescence was uneventful.

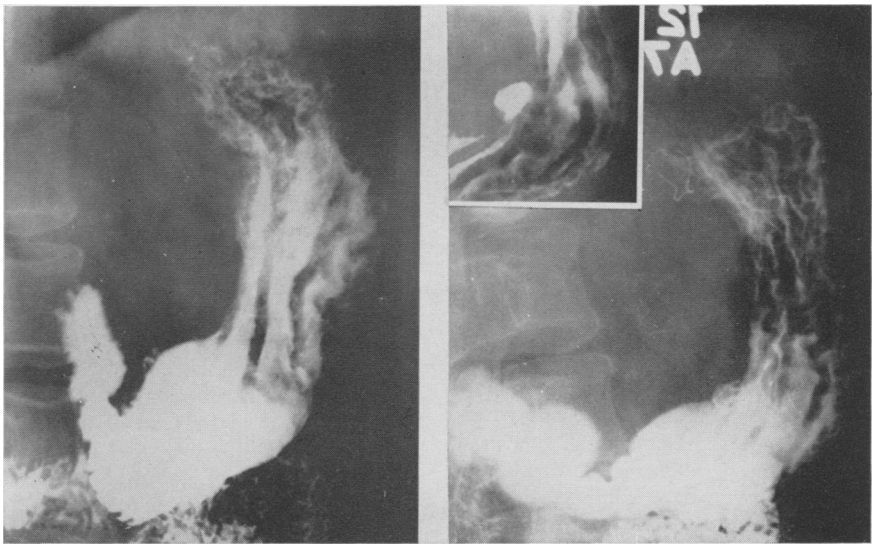

FIG. 1 (Left). Gastroduodenal x-ray of O. W. B. (Case 1) taken March 6, 1951 before portacaval shunt. No ulcers are seen.

FIG. 2 (Right). X-ray of O. W. B. taken December 14, 1951, nine months after portacaval shunt. There is a lesser curvature gastric ulcer.

The patient came to the Veterans Administration Center, Los Angeles, on March 21, 1957 due to recurrence of his previous burning epigastric ulcer pain. This rapidly disappeared on antacids, bland diet and frequent feedings of milk, but this treatment was followed by progressive lethargy and finally coma. At this time the liver function tests were moderately impaired, but blood ammonia was never elevated. With carbohydrates, oral antibiotics, and intravenous arginine the coma abated, and a 35 Gm. protein diet was tolerated well. The patient was re-admitted in May and in October 1957 with recurrent episodes of stupor. These were controlled on a strict 25 Gm. protein diet. Each time the typical ulcer pain had recurred as the stupor had regressed. Moreover at home the ulcer pain occurred two to three times a week, and sometimes awakend the patient nightly. At present he is doing well by taking antacids hourly and following the low protein diet. There has been no bleeding since the shunt. Three x-rays over the past nine months have shown minimal varices, but a tender, deformed, irritable duodenal cap, interpreted as diagnostic of active duodenal ulcer.

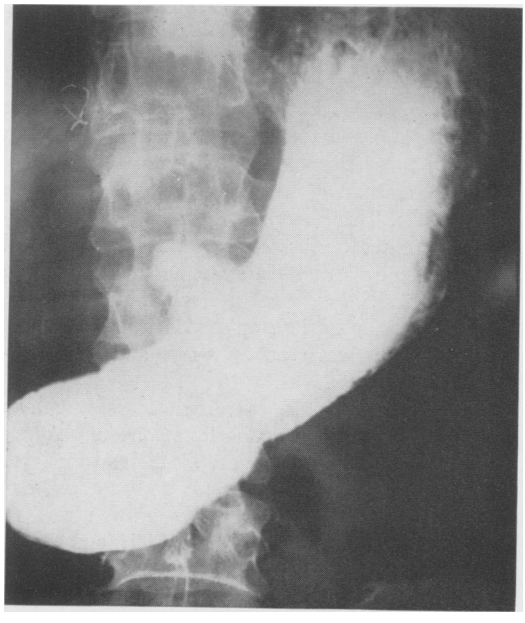

FIG. 3. X-ray of O. W. B. taken January 23, 1953. There is marked retention and a huge gastric ulcer.

Discussion

It is worth noting that in each of the above cases the ulcer symptoms originated within nine months after formation of the portacaval shunt. Four of the five men had nothing to suggest ulcer disease before the shunt. There were four duodenal ulcers and

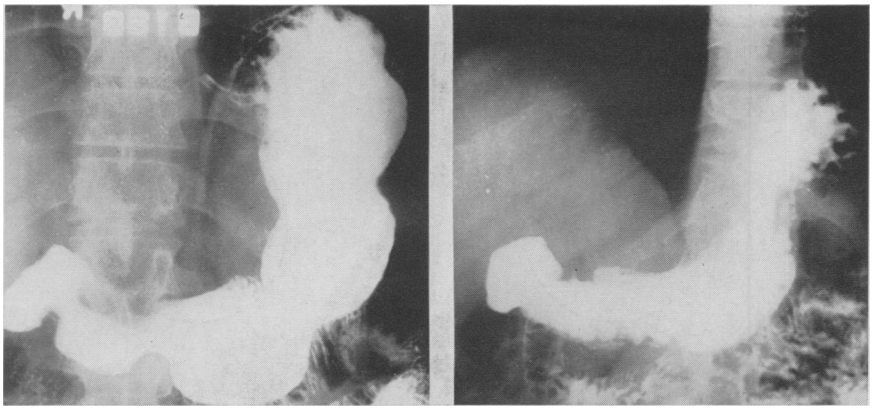

FIG. 4 (Left). Gastroduodenal x-ray of C. R. W. (Case 2) taken January 22, 1953 before portacaval shunt. Esophageal varices are seen, but there is no gastric or duodenal ulceration.

FIG. 5 (Right). X-ray of C. R. W. taken July 20, 1953, three months after portacaval shunt. There is an ulcer crater on the superior margin of the prepyloric area of the stomach.

two gastric ulcers, patient C. R. W. (Case 2) showing first a prepyloric ulcer and later a duodenal ulcer. The ulcer disease was in general very severe. It required gastric resection for control in one patient (Case 1) and led to death from hemorrhage in two (Cases 2 and 3).

The question naturally arises as to the role of continued consumption of alcoholic beverages in the etiology of these ulcers. As far as we can ascertain none of the five patients drank excessively after his shunt except O. W. B. (Case 1), who did return to drinking 18 months after gastric resection for gastric ulcer. In three (Cases 1, 2 and 4) the cirrhosis was secondary to alcoholism, but in Case 3 it was due to hepatitis and in Case 5 the cause could not be determined. Therefore excessive alcoholic intake is probably not the cause of post-shunt ulcers.

The significance of the occurrence of these five cases of ulcer disease in the early post-shunt period is hard to assess. We have not determined how many of these 62 patients had ulcer symptoms before their shunts, and additional instances of post-shunt ulcer may well appear as time passes. The incidence of ulcer after shunt in this group of patients is at least five out of 62, or 8 per cent, and may become larger. Interpretation of the significance of the shunt itself in relation to the ensuing ulcer disease is complicated by at least three factors. First, the incidence of ulcers in patients with cirrhosis is probably increased, as noted previously. Second, the incidence of ulcers in cirrhotic patients who are chosen for shunts is not precisely known. Third, patients with cirrhosis have a varying degree of shunting of portal blood around the

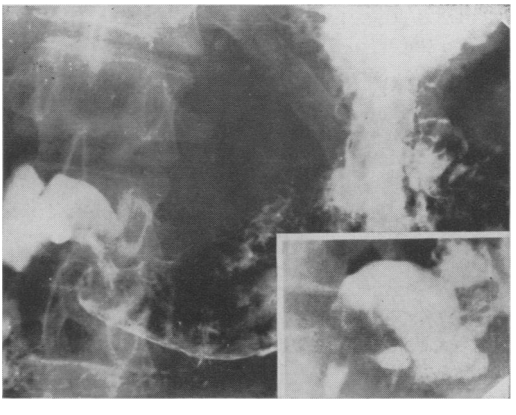

FIG. 6. X-ray of C. R. W. taken October 20, 1953. The gastric ulcer has healed, but there is a new ulcer in the duodenal cap.

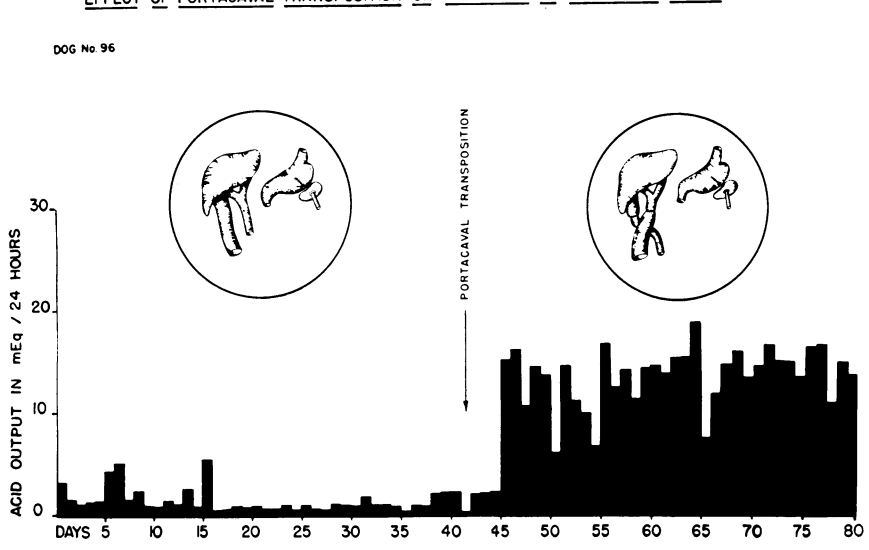

FIG. 7. Illustrative experiment showing marked increase in HCl output from Heidenhain pouch of Dog. No. 96 after portacaval transposition.

liver, regardless of whether they have been subjected to an operative portacaval anastomosis. Despite the above considerations, we feel that the development or aggravation of ulcers in these five patients, their occurrence soon after shunt, and their severity, strongly suggest a causal relationship.

2. Experimental Observations

A number of theories have been suggested to explain the occurrence of ulcers in cases of hepatic dysfunction. Among those cited by Bockus [5] were malnutrition, decreased amounts of biliary elements, central nervous system damage, and inflammation and congestion of the gastric mucosa. Bockus also stated that most cases of advanced liver disease are associated with a gastric secretory deficiency. Recent studies on gastric secretion in patients with cirrhosis are few, but Lebedinskaja [20] reviewed six pertinent reports appearing between 1893 and 1901 in the European literature. The authors he cited found elevated acidity of the gastric content in cases of jaundice and of cirrhosis, but in some cases, particularly far advanced ones, gastric acid was low or absent.

Baronofsky and Wangensteen [2] demonstrated in the dog and rabbit that portal or splenic vein obstruction caused increase in the weight of the stomach, edema of the gastric wall, and formation of esophageal varices. When histamine in beeswax was given to such animals they soon developed large gastric ulcers or erosions, whereas control animals did not. Thus obstruction of the venous drainage from the stomach predisposed the animals to ulceration, presumably due to the edema of the gastric mucosa.

Our animal experiments were designed to determine whether diversion of portal venous blood around the liver results in an increase in secretion of acid by the stomach. When an increase was found, additional experiments were done in an effort to clarify its mechanism.

Methods: Heidenhain pouches were fashioned from the greater curvature of the stomach in nine mongrel dogs weighing between 12 and 24 Kg. The spleen was not removed. The nerves coursing along the

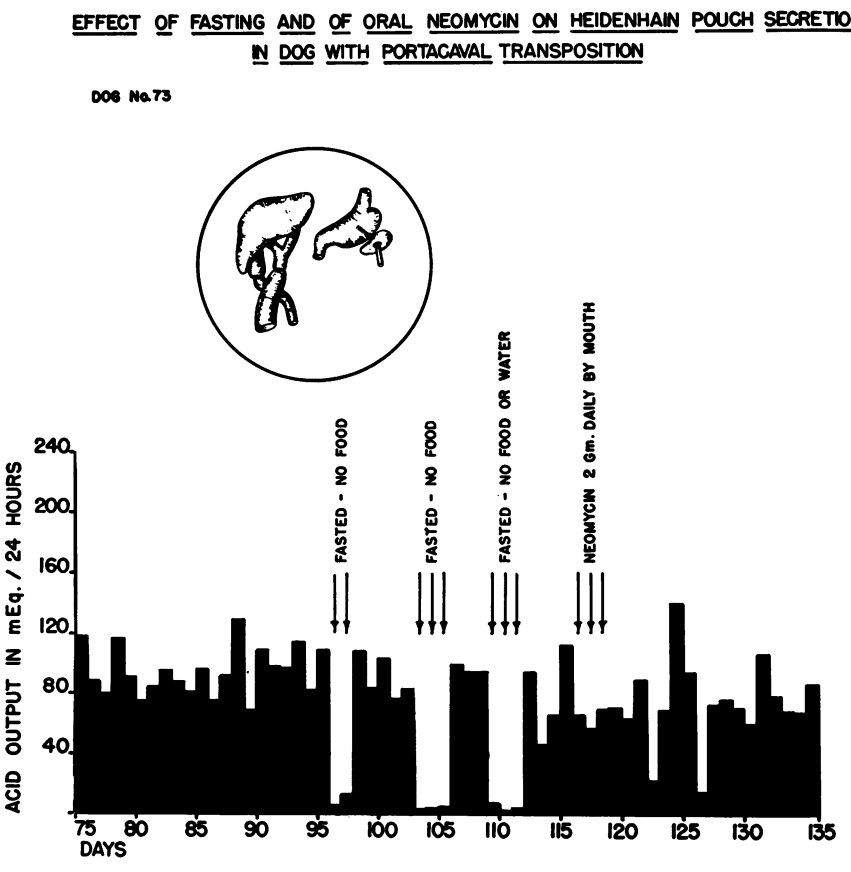

FIG. 8. Illustrative experiment on Dog. No. 73 who had Heidenhain pouch and portacaval transposition. Fasting depressed HCl output, but oral neomycin did not affect it.

vascular supply of the completed pouch were not interfered with, but the major innervation from the vagal trunks was necessarily divided. Each pouch was drained by an inlying stainless steel cannula into a rubber football bladder, allowing quantitative collection of the pouch secretion for each 24-hour period as described by Dragstedt and his co-workers.[11] The volume of each 24 hour collection was measured, and its free acid concentration in milliequivalents per liter determined by titration with 0.1 N NaOH to the color change of Toepfer's reagent. The total HCl output was calculated. Each dog was fed a constant amount, varying from two to four cans in different dogs, of a commercial dog food (Trade name Thoro Fed) during the entire experiment. Water was allowed *ad lib.* The diet was supplemented daily by 1 Gm. of NaCl for each 100 ml. of pouch secretion.

After 30 to 42 daily collections each dog was subjected to a portacaval transposition operation as described by Child.[7] All tributaries of the portal vein were divided from the junction of the superior mesenteric and splenic veins to the portal bifurcation at the hilum of the liver. The right adrenal vein was ligated and divided, and the inferior vena cava was freed up from this level to its entrance into the liver. The portal vein and inferior vena cava were then transected, transposed, and the cut

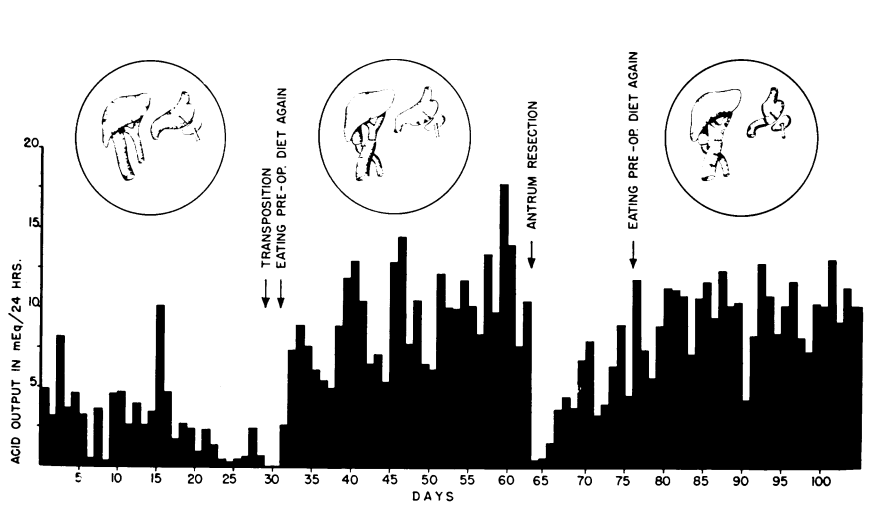

FIG. 9. Illustrative experiment on Dog. No. 7. Heidenhain pouch secretion of HCl increased after portacaval transposition. It was unchanged after antrum resection.

ends were anastomosed end-to-end. As a result the portal vein drained into the cephalad cut end of the inferior vena cava, completely by passing the liver, while the caudal portion of the inferior vena cava drained into the cepahalad cut end of the portal vein, giving a large flow of systemic venous blood to the liver. As soon as the dog was eating the same amount as before operation collections were resumed and continued for 24 to 42 days.

Twelve studies were done to assess the effect of fasting on Heidenhain pouch secretion in dogs with portacaval transposition. The mean average of the 24-hour acid output for three days on the usual diet was determined. This was compared with the average acid output for the subsequent

TABLE 1. *Secretion from a Heidenhain Pouch Before and After Portacaval Transposition*

Dog Number	Number of 24-Hour Collections		Mean Acid Output in mEq./24 Hours		Per Cent Increase
	Before	After	Before	After	
7	39	32	4.18 ± 3.25*	9.42 ± 3.29	125
14	30	40	1.68 ± 1.43	6.89 ± 5.6	310
16	38	30	15.81 ± 7.71	59.38 ± 23.72	276
29	37	26	24.57 ± 12.07	47.28 ± 12.97	92
73	39	42	23.6 ± 9.1	94.1 ± 26.5	299
74	35	24	25.8 ± 14.1	101.9 ± 58.6	295
95	42	30	2.6 ± 1.4	19.1 ± 8.0	635
96	40	35	1.4 ± 1.2	13.3 ± 2.8	850
136	30	26	5.18 ± 2.74	16.17 ± 8.28	212
Mean Average			11.7	40.8	344

* Standard deviation of the mean.
$P < .005$ by the Sign Test.[10]

three days during which no food was given, but water was allowed *ad lib*. Four of these 12 studies were done on dogs who had antrum resection in addition to portacaval transposition.

Nine experiments were done to determine the effect of daily oral administration of neomycin in doses of 1.5 to 6.0 Gm. on acid output in dogs with transposition. The diet was the same during the three day control period as during the following three days on neomycin. The neomycin was mixed in the food, and no laxatives were used.

Two dogs were subjected to resection of the pyloric antrum and end-to-end gastroduodenostomy after the pouch secretion of acid in the presence of transposition had been measured. Collections were resumed when they were eating as before resection, and were continued for 29 and 30 days.

Results

Portacaval transposition resulted in a prompt, consistent, and striking increase in acid secretion from the Heidenhain pouch. The data are set out in Table 1 and an illustrative experiment is shown in Figure 7. In general both volume and acidity of the pouch secretion were augmented. The range of the per cent increase was 92 to 850, and its mean was 344. The highest increase occurred in dogs who were low secretors before transposition. Data on four of these dogs have been presented previously in a preliminary report.[8]

TABLE 2. *Secretion from a Heidenhain Pouch Before and During Fasting in Dogs with Portacaval Transposition*

Dog Number	Mean Acid Output in mEq./24 Hours Over 3-Day Period: Before Fasting	During Fasting	Per Cent Decrease
0	59.8	6.8	87
0	35.7	4.1	89
7	12.3	3.3	73
7	12.9	5.6	57
14	9.5	2.0	74
14	4.7	3.7	21
14	4.9	2.4	51
16	52.4	9.7	81
73	87.8	4.0	95
73	96.8	4.4	95
74	1.3	0	100
136	20.0	15.5	23
Mean Average	33.2	5.1	71

$P < .005$ by the Sign Test.[10]

TABLE 3. *Secretion from a Heidenhain Pouch Before and During Administration of Oral Neomycin in Dogs with Portacaval Transposition*

Dog Number	Mean Acid Output in mEq./24 Hours Over 3-Day Period: Before Neomycin	On Neomycin	Dose of Neomycin in Grams per Day
0	42.0	66.5	2
7	7.7	10.9	6
7	15.8	15.9	6
14	9.8	12.5	1.5
14	8.7	4.9	6
14	4.3	3.6	6
16	42.1	36.9	6
73	75.1	66.0	2
74	3.1	4.9	6
Mean Average	23.2	24.7	

Fasting caused a prompt and marked fall in acid secretion. The data are given in Table 2 and an illustrative experiment shown in Figure 8.

Administration of neomycin by mouth in doses of 1.5 to 6.0 Gm. along with the usual diet did not appear to have any consistent effect. The data are given in Table 3 and a representative experiment is shown in Figure 8.

The data on two dogs who underwent antrectomy after portacaval transposition are given in Table 4. It will be seen that resection of the pyloric antrum had very little effect on the increased Heidenhain pouch secretion induced by transposition. Figure 9 shows one of these experiments.

All of the dogs lost weight slowly dur-

TABLE 4. *Secretion from a Heidenhain Pouch Before and After Portacaval Transposition and Subsequent Antrum Resection*

Dog No.	No. of 24-Hour Collections			Mean Acid Output in mEq./24 Hours		
	Before Trans.	After Trans.	After Resection	Before Trans.	After Trans.	After Resection
7	39	32	30	4.18 ± 3.25*	9.42 ± 3.29	9.84 ± 2.05
14	30	40	29	1.68 ± 1.43	6.89 ± 5.6	5.87 ± 2.19

* Standard deviation of the mean.

ing the experiment. At the present time only Dog No. 7 is still alive. At autopsy all the others had open portacaval transpositions and grossly normal livers. Clinically no dog showed signs of hepatocerebral intoxication or coma. Two dogs (Nos. 73, 95) died due to perforating ulcers in their pouches. Dog No. 96 died seven days after antrum resection with a perforated gastric ulcer on the anterior wall of the stomach. Dog No. 70, who is not included in the tables, died eight days after transposition with a 1.5 × 2.0 cm. perforated gastric ulcer high on the greater curvature and a left subdiaphragmatic abscess. Three dogs (Nos. 0, 16, 136) died a few days after antrum resection from complications of this operation. Dog. No. 14 became progressively debilitated and died without evident gross anatomic cause. Dog No. 29 died of small bowel obstruction and acute gastric dilatation. Dog No. 74, who was small, became dehydrated due to huge volumes of pouch secretion, and died of fluid loss and anorexia 24 days after transposition.

Discussion

The earliest experimental demonstration that we have found of the increase in gastric acid secretion following diversion of portal blood around the liver is that of Lebedinskaja [20] in 1933. He prepared two dogs with vagally innervated gastric pouches and later made an Eck fistula in each. Utilizing milk, meat, bread, and Liebig's extract test meals, he found a profound increase in volume and acidity of the pouch secretion, prolongation of the duration of secretion, and a marked decrease in peptic activity after formation of the Eck fistula. These findings were confirmed by Gerez and Weiss,[14] who measured the secretion from Pavlov pouches in response to a meat meal in three dogs before and after making Eck fistulas. They concluded that substances are present in portal blood which influence gastric secretion, and that the liver normally retains or destroys these substances to some degree.

R. A. Gregory [15] published in 1957 interesting studies on dogs with gastric cannulae and denervated gastric pouches. He ligated the portal vein above its highest tributary with Cellophane tape as described by Grindlay and Mann,[16] causing gradual occlusion of the vessel by fibrosis without ensuing liver atrophy. After operation the volume and acidity of pouch secretion after a meal were increased. Moreover the maximal response of the pouch to histamine stimulation gradually increased to about twice its preoperative level. In some dogs the pouch response began within 15 minutes of eating, and even sham feeding or teasing with food caused a considerable secretion from the pouch. He felt that these findings proved that a stimulant of gastric secretion is released into the portal blood by vagal excitation, and that whether this stimulant survives passage through the liver is open for discussion.

A significant contribution to this problem by Dubuque, Mulligan and Neville [12] appeared recently. They found a threefold in-

crease in 24 hour acid output from Heidenhain pouches in dogs after side-to-side portacaval shunt and ligation of the portal vein close to the liver. Results were similar in other dogs who had partial portal vein ligation with umbilical tape, allowing gradual occlusion; and the elevation remained unchanged when subsequent portacaval anastomosis was done below the site of occlusion. They also found that daily histamine stimulation caused death from duodenal ulcer much sooner and with far greater frequency in dogs with portacaval shunts or portal ligation than in normal controls. They suggested that an agent from the liver or one whose metabolism in the liver is decreased may be responsible.

The stimulating effect of portacaval transposition on Heidenhain pouch secretion in the dog is firmly established on the basis of the data presented in Table 1. In forming a Heidenhain pouch the vagus nerves running over the stomach to the pouch are cut. The secretion from such a pouch is largely in response to humoral agents as demonstrated by its low levels after antrum resection.[28] Therefore the increase in secretion found in these experiments is probably of humoral origin.

Three broad possibilities suggest themselves to explain the findings. Under appropriate conditions of diminished or altered blood flow the liver itself might produce a humoral stimulant to gastric acid secretion. Second, a secretogogue might be released into the portal vein from any one or from several of the organs it drains, this agent being inactivated or excreted by the liver under normal conditions. Finally an inhibitory humoral substance might be released into the portal blood and require activation in the liver.

We chose portacaval transposition in this study because it provides complete shunting of portal blood around the liver and still causes minimal impairment of hepatic function. Child and co-workers [7] found that hepatic regeneration was absent in dogs with Eck fistulas, and was good, though not entirely normal, in dogs with portacaval transpositions. Silen *et al.*[25] concluded after careful studies that the function and histologic appearance of livers of dogs with transpositions were very similar to those of normal animals. Tolerance to oral ammonium lactate was of course diminished in dogs with Eck fistulas and in others with transpositions, but this was much more marked in the former. Thus the observed increase in pouch secretion after transposition probably is not due to impairment of parenchymal liver function and need not be associated with the reduction in hepatic venous blood flow which occurs in the Eck fistula. The possibility that the liver produces a secretogogue because it is affected by an altered blood supply therefore seems unlikely, though it is not completely ruled out.

Our experiments bear on the second possibility, that a secretory stimulant is released into the portal venous system and normally is inactivated in the liver. Our fasting experiments, as well as the feeding tests of Lebedinskaja,[20] Gerez and Weiss,[14] and Gregory,[15] show that increased Heidenhain pouch secretion after transposition is closely related to ingestion of food. As seen in Table 2, secretion fell markedly, usually to low levels, during fasting. Gregory's observations that the pouch secretion may begin within 15 minutes after eating and that it may be considerable during sham feeding suggest that the psychic phase may play a role, possibly through the release of gastrin. The relatively small decrease in pouch secretion during fasting in a few of our dogs, especially No. 136, could be due to psychic stimulation of the fasted dog when food was distributed in a large common animal room.

The antrum resection experiments were designed to see whether gastrin might be the humoral agent involved. As shown in Table 4 antrum resection did not significantly alter the increased output of HCl

by the pouch in two dogs with transposition. Either gastrin is not important or antrum resection itself somehow increased pouch secretion in these dogs, thus obscuring a depression in output which would have otherwise been evident. More antrum resection experiments are needed with special care to ensure good emptying of the gastric remnant.

The neomycin experiments were intended to assess whether some product of bacterial action in the bowel, such as ammonia, is responsible. The results in Table 3 show no consistent effect of large doses of oral neomycin, given with the food and without purgation, on pouch secretion. Any interpretation of these findings with reference to the organisms in the gut is vitiated by our finding that in two dogs, on whom stool cultures were done after three days on 6 Gm. daily of neomycin, there was relatively little depression of the bacterial flora. Aerobic gram positive bacilli were completely suppressed, but coliforms were unchanged in Dog No. 14 and fell from 10^7 to 10^3 per gram of feces in Dog No. 7. Enterococci fell only from 10^7 to 10^5 per gram in No. 14, and from 10^7 to 10^1 per gram in No. 7. Therefore neomycin as given had no effect on pouch secretion, but we cannot conclude that effective sterilization of the bowel does likewise.

One theory consistent with the experimental findings is that the hypersecretion after portacaval transposition is due to secretogogues absorbed from or formed by the small intestine during digestion. The liver metabolizes at least in part the products of digestion presented to it in the portal blood, some of which are known secretogogues. Thus transposition may unmask and augment the intestinal phase of gastric secretion.

It seems remarkable to us that on one hand peptic ulcers are frequent in patients with cirrhosis of the liver and with portacaval shunts, and that on the other hand Heidenhain pouch secretion in dogs is profoundly elevated when portal blood bypasses the liver. More studies, particularly concerning gastric secretion in response to feeding in appropriate patients, are required to establish whether this is more than a mere coincidence.

Summary

1. Five cases of post-shunt ulcer are reported from a total group of 62 portacaval shunt patients. Four patients had no evidence of ulcers before shunt; the fifth had worsening of a pre-existing ulcer after shunt.

2. In dogs the secretion of acid from a Heidenhain pouch was profoundly increased after portacaval transposition. This increase was markedly reduced by fasting, unaffected by giving oral neomycin, and persisted after resection of the gastric antrum.

3. This may be due to the increased effect, after shunting of portal blood around the liver, of a humoral secretogogue which originates in the abdominal viscera and is normally inactivated by the liver.

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Discussion

DR. LESTER H. DRAGSTEDT: Dr. Gilchrist, Ladies and Gentlemen: I have followed this work of Dr. Clarke and his associates with a great deal of interest. It seems to me that he has described and discovered a new clinical entity, and the scientific basis for it. It is additional evidence that peptic ulcers can be produced in an entirely normal mucous membrane by a hypersecretion of gastric juice.

The old idea of a local decrease in resistance is gradually receding, I think, into the background.

When we first learned about this work of Dr. Clarke, Dr. Kohatsu and Dr. Gwaltney repeated the experiments which Dr. Clarke has described, and in each case confirmed them. Hypersecretion continued even after the antrum was removed, which is a very interesting phenomenon.

Now, it is quite possible that when the blood from the intestinal tract is diverted away from the