S^{35}-L-methionine 2 days prior to wounding is incorporated into wound tissue in large measure as protein-bound methionine and cystine. 4. During the interval studied, administered methionine-S^{35} is not a precursor for wound tissue mucopolysaccharide sulfate.

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Received September 27, 1957. P.S.E.B.M., 1958, v97.

Sensitivity of the Common Bile Duct to Acid Peptic Digestion.* (23706)

E. G. YONEHIRO, K. IMAMOGLU, H. D. ROOT, N. W. CRISP, S. L. WANGENSTEEN, AND O. H. WANGENSTEEN

University of Minnesota Medical School, Department of Surgery, Minneapolis

Narrowing of the terminal biliary papilla as it enters the duodenal lumen has been observed in more than 50% of patients operated upon for gallstones(1). The causes for such narrowing are not apparent. The purpose of this study is to evaluate the sensitivity of the mucosa of the common bile duct to injury by acid-peptic juices, as the biliary component of the papilla does project into the duodenal lumen and could there be subjected to periodic submergence in gastric juice. If the bile duct epithelium proved sensitive to acid-peptic digestion, it is possible that erosive injury may play a role in bringing about the narrowing of the papilla observed so frequently in patients with gallstones. The recurrent stricture following choledochoduodenostomy could also find an explanation in such an occurrence. These considerations suggested the need to test the sensitivity of the mucosa of the common bile duct to acid-peptic digestion by perfusion with human gastric juice, with acid-pepsin mixtures, and with pancreatic juice and bile mixtures.

* Supported by grant from U.S.P.H.S., Jay and Rose Phillips Research Fund and Arthur and Stella Sanford Fund.

Method. Adult cats were anesthetized with approximately 26 mg/kg body weight of sodium pentobarbital given intraperitoneally. Simultaneous perfusions of the esophagus and common bile duct were carried out. The sensitivity of the esophageal mucosa to injury by acid-peptic juice is well known(2) and concomitant perfusion of that organ could serve as a useful control. The gastric juice employed in the perfusion had been obtained from fasting patients by an inlying gastric tube attached to suction overnight for an 8-hour period from 11:00 p.m. to 7:00 a.m. Patients with peptic ulcer, cholelithiasis, as well as those with normal gastrointestinal tracts were studied. Gastric secretions were collected on ice and either analyzed immediately or frozen and stored below 0°C until used. The volume was measured and determinations of pH, free acid and pepsin were made. The pH was measured with the Northrup & Leeds glass electrode, free HCl was determined by titration with 0.1 N NaOH, and pepsin was determined by the hemoglobin substrate method of Anson(3). The gastric juice was adjusted to pH 1.6-1.7 at which acidity, optimal peptic activity is achieved. Commercial pepsin and acid solu-

tions were also made up and used as perfusing solutions in the same manner. In addition, human pancreatic juice as well as bile were perfused without changing the pH of the solution. Admixtures of human pancreatic juice and bile in a one to one ratio were then incubated for varying periods of time (½ to 48 hours) at 37°C prior to its use as an additional perfusing solution. The pancreatic juice was obtained from a patient with chronic pancreatitis whose pancreatic duct was cannulated for drainage and decompressive purposes at surgery. The specimens were collected on ice, cultures were obtained and the juice frozen immediately. Amylase, tryptic and lipase activities were determined before perfusion. All bile specimens used in the study were collected via a T-tube inserted at the time of common bile duct explorations. Perfusion of esophagus was performed as previously described(4). The common bile duct was perfused by cannulating the cystic duct near its entry into the common duct and ligating the major hepatic ducts proximally to preclude the retrograde flow of bile into the proximal reaches of the hepatic ducts. On occasions, one or both of the hepatic ducts were left open. The duodenum was then cannulated distal to the ampulla of Vater. In every instance the pylorus was occluded to prevent flow of gastric contents into the duodenum during the perfusion. The tubing carrying the perfusate to the cat was passed through a 37°C water bath to maintain constant temperature. Perfusion was carried out at a rate of 2-3 cc min. (40-50 gtts min.) under a pressure of 20 to 40 cm of water for 2 hours. Simultaneous perfusions of the esophagus and the common bile duct of the living anesthetized cat were carried out. The 2-hour end point in the esophagus has proved very practical in assessing the sensitivity of the esophageal mucosa to injury by digestive juices. Perfusions in the first 4 instances, however, were carried out for up to 20 hours. We had not anticipated finding the bile duct mucosa as sensitive to digestion by acid-peptic juice as the esophagus. The animals were then sacrificed and the degree of digestion produced graded zero to five +. (1 + = erosion of the mucosal epithelium; 2 + = erosion into the submucosa; 3 + = digestion into the muscular layers; 4 + = impending perforation with only serosa being intact; 5 + = perforation.)

TABLE I.

A. Source of gastric juice Patient's diagnosis	No. of cats	Actual perforation or 4+ digestion	
		CBD	Esophagus
Cholelithiasis	6	3	2
CBD stone	1	—	—
Duodenal ulcer	18		
Pre-op.	9	8	6
Post-op.	9	1	2
Ca. of stomach	1	0	1
Miscellaneous	4	1	0
Total	31	13	11
B. Commercial pepsin sol.	3	3	3
HCl solution (0.1 N)	3	0	0
Human bile	2	0	0
Pancreatic juice	2	0	0
C. Human bile and pancreatic juice			
a Incubated ½ hr	3	0	0
b 12	2	0	0
c 24	6	0	0
d 36	3	0	0
e 48	3	0	0

Results. Over one-third of the animals studied had either severe digestion or perforation of the common bile duct during the perfusion period (Table I A). A like number of esophageal perfusions resulted in comparable degrees of digestion. Of 31 cats in which perfusions were carried out, actual perforation (5 +) or severe digestion (4 +) of the common duct was seen in 13 instances. Simultaneous esophageal perfusions performed demonstrated similar changes in 11 cats. In 3 animals perforations of both the common bile duct and esophagus occurred.

When the common duct was perfused with 0.1 N HCl, little damage was seen, but the addition of 1.2 mg/cc pepsin to the perfusate regularly produced severe digestion (Table I B).

Investigators have recently demonstrated that bile and pancreatic juice in a 1 to 1 mixture when incubated for 12-48 hours and perfused in the pancreatic duct produced a lethal hemorrhagic pancreatitis in 100% of the animals (dogs) studied(5). Such mixtures were also evaluated in this study since obstruction

of a common channel at the sphincter of Oddi is occasionally seen in patients with biliary tract disease. Perfusion of the common bile duct with this solution demonstrated relatively little digestion ranging from 0 to 2 + (Table I C) over the 2-hour period of the study. On one occasion a 3 + erosion was noted. Whether one or both of the major hepatic ducts were ligated did not appear to influence the degree of digestive changes.

Summary. 1. The glandular mucosa of common bile duct shows a sensitivity to acid-peptic digestion at least as great as that of the esophagus. 2. Admixture of bile and pancreatic juice incubated from ½ to 48 hours failed to demonstrate evidence of digestive injury to either the common bile duct or the esophagus during a 2-hour period of perfusion. 3. There would appear to be a possibility that acid-peptic erosion of the biliary papilla may play a role in the genesis of stricture of the bile duct in some disease states.

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Received November 25, 1957. P.S.E.B.M., 1958, v97.

Tolerance and Withdrawal Hyperexcitability Induced in Mice by Chronic Administration of Phenaglycodol.* (23707)

LINCOLN CHIN AND EWART A. SWINYARD (Introduced by Louis S. Goodman)

Departments of Pharmacology, University of Utah College of Pharmacy and College of Medicine, Salt Lake City

Several clinical reports(1-5) reveal that abrupt withdrawal of meprobamate (Miltown, Equanil) medication in patients who have ingested large doses of this drug may precipitate nervousness, insomnia, and convulsions. Work in our laboratories(6) indicates that tolerance and withdrawal hyperexcitability result from chronic administration of large doses of meprobamate to mice, as measured by the technic of McQuarrie and Fingl(7). Tolerance and withdrawal convulsions were also observed to occur after administration of large doses of this drug in dogs, by Essig and Ainslie(4). Since both meprobamate and phenaglycodol (Ultran) are substituted propanediols and have similar pharmacological activities in experimental animals(8,9), it was of interest to determine the effect of chronic administration of large doses of phenaglycodol and of its subsequent abrupt withdrawal on central nervous excitability in mice. In the absence of positive evidence that this drug induces tolerance and physical dependence in man, it was anticipated that such a study might predict the effects of abrupt withdrawal of phenaglycodol in patients who have been chronically ingesting large doses. The results obtained provide the basis for this report.

Methods. Male albino mice (Carworth Farms, CF #1 strain, 21 to 32 g in weight) were randomly divided into 2 groups of 50 animals each. Phenaglycodol† was administered orally to one group as a 2 or 3% suspension in 6% acacia solution, in a total daily dose of 600 mg/kg (200 mg/kg at 7 a. m., 3 p. m., and 12 midnight) for 6 days. Because of the development of tolerance, following the 7 a. m. treatment on day 7 each dose was increased by 50% to make a total daily dose of 900 mg/kg; this higher daily

* This investigation was supported by grant (B-381) from Nat. Inst. of Neurological Diseases and Blindness, N.I.H., P.H.S.

† Kindly supplied by Dr. K. K. Chen, Eli Lilly and Co.