biologically is not all available to the mouse.

No explanation is offered for the appearance of acrodynia in our experiments in contrast to the usual freedom in mice from acrodynia during pyridoxine deprivation. By inspection of the conditions of previous studies of B_6 deficient mice together with the variables introduced in our experiments, no definite correlation could be established relating the composition of the diet, age or sex of the mice, the probable pyridoxine content of the diet, levels of other vitamins, etc., to the protection from, or appearance of, acrodynia. The syndrome has appeared in the mice without fail on 3 different occasions that were so spaced in time (February, May, and September) that such factors as season and humidity were probably not involved. Only one strain of mice was tested, and it may be that strain differences play an important role in the appearance of acrodynia.

Summary. 1. Pyridoxine deficiency was produced in weanling male and in young adult female mice fed (a) a purified diet containing 9 other crystalline B vitamins, and (b) a semipurified diet containing a low level of liver powder. 2. Acrodynia appeared among both the weanling and young adult mice fed these 2 diets. 3. As little as 0.166 mg of added crystalline pyridoxine-HCl per kg of the purified diet protected the mice from acrodynia and resulted in a good growth response by the weanling mice.

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Role of Bile and Pancreatic Juice in Production of Esophageal Erosions and Anemia.* (18950)

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Numerous studies have been carried out on the ability by trypsin to digest living tissues and on the toxic effect of bile salts on certain tissues. Claude Bernard(1) showed that the leg of a living frog was digested away when introduced into the stomach of a dog. Rosenbach(2) produced hemorrhages on the tongue of a frog by the local application of a solution of active trypsin. Langenskjöld(3) found he could cause ulceration and necrosis of urinary bladder mucosa in the dog by perfusing it with pancreatic juice, but not to the degree produced by gastric juice. Kirchheim and Böttner(4) found no changes in the mucous membrane of the urinary bladder, esophagus or intestine after exposure to active trypsin solution for 10 hours. Necheles and associates(5) and Dragstedt and associates(6) implanted various organs such as pancreas, kidney, liver and omentum into the duodenum exposed to active pancreatic ferments and found in most cases no digestion of these organs. Rywosch(7) was one of the first investigators to point out the toxic effect of bile salts on various tissues. Opie(8) and Flexner(9) showed the destructive effect of bile

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and bile salts on the pancreas, and Smith(10) on the gastric mucosa. The present study was prompted by recent work demonstrating the susceptibility of the esophagus to injury by acid-peptic juice(11), and by the circumstance that patients who undergo total gastrectomy often complain of symptoms occasioned by the regurgitation of bile into the esophagus.

Present study. Two sets of experiments were carried out, the first on cats, and the second on dogs. In cats weighing 1.4 to 3.5 kg under nembutal anesthesia, the esophagus was perfused with mixtures of bile and pancreatic juice, bile alone, pancreatic juice alone and intestinal juice collected from dogs. Also, perfusing solutions of human bile and of bile salts in a concentration of 0.65 g of bile salt for each 5 cc of normal saline were used. A cannula was tied into the cervical esophagus and another into the stomach just beyond the esophago-gastric junction. The perfusing solution at a temperature of 38° was dripped from a burette into the proximal cannula at a rate of 25 cc per hour until the cat died, but no longer than 8 hours. The pressure of the solution in the esophagus was not allowed to exceed 20 cm of water. The juice used for the perfusions was collected from duodenal fistulae in dogs, some of which drained bile and pancreatic juice, and others of which drained only pancreatic juice. Bile was collected from dogs by means of a cholecystostomy tube, and succus entericus was obtained from a 45 cm loop of duodeno-jejunum. Human bile was collected from patients at the time of autopsy, or from patients who had been on T-tube drainage of the common bile duct for not more than 2 days. The mixtures containing pancreatic juice were collected at frequent intervals and frozen to prevent loss of tryptic activity. The activity of these juices was tested at the time of each perfusion by the modified method of Fermi(12). None of the bile, collected either from dogs or humans, showed tryptic activity.

The second set of experiments was carried out on mongrel dogs weighing 9 to 18 kg. Duodeno-esophagostomies, cholecystojejuno-esophagostomies, jejuno-esophagostomies, and total gastrectomies with end to end duodeno-esophagostomies were made to cause diversion or regurgitation of bile and pancreatic juice, pancreatic juice alone, bile alone, and succus entericus into the esophagus. The dogs were esophagoscoped within 8 to 14 days after the initial operation and were followed at frequent intervals by esophagoscopy to ascertain the degree to esophagitis developing. Complete blood counts were taken each week, and stools were studied for occult blood during periods when the dogs were on a meat free diet. The dogs were sacrificed after a period of 1 to 3 months. To rule out postmortem autolytic changes produced by the bile and pancreatic juice, only those dogs autopsied immediately after death were counted in the series.

Results. A. Cats. The criteria for grading the degree of esophagitis produced in cats are outlined in the footnote of Table I. From this table it can be seen that, in general, perfusions with mixed bile and pancreatic juice caused the most severe changes, and pancreatic juice alone caused only minimal changes.

TABLE I. Perfusion of Esophagus in Live Cats with Various Juices.*

Type of juice	No. of cats	Severe changes	Minimal changes	No changes
Mixed bile and pancreatic juice	19	12	6	1
Bile only	14	7	4	3
Pancreatic juice only	10	1	9	0
Sodium taurocholate or sodium glycocholate	8	8	0	0
Jejunal juice	5	0	0	5
Human bile	6	5	1	0

* Criteria for grading esophagitis in cats: *Severe esophagitis*: 1. definite ulcerations; 2. marked discoloration of mucous membrane with many erosions and petechiae; 3. fluid in mediastinum or thoracic cavity. *Minimal esophagitis*: 1. a few erosions and petechial hemorrhages; 2. discoloration of mucous membrane in addition to No. 1; 3. no ulcers, no fluid in mediastinum or thoracic cavity. *No changes*: 1. mucosa merely bile-stained. None of changes outlined above.

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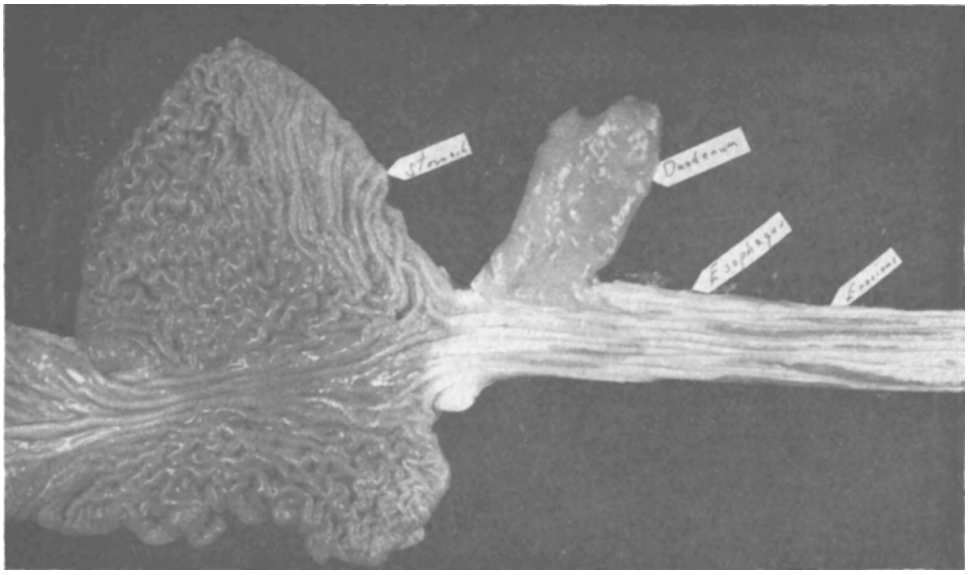

FIG. 1. Esophageal erosions produced by the diversion of bile and pancreatic juice into the esophagus following duodeno-esophagostomy.

In the former, the esophagi were greenish-brown, almost black, in appearance with numerous erosions and areas of hemorrhage after periods of perfusion lasting 3 to 8 hours. In the latter, the only changes were reddening of areas of the mucosa and a few erosions. In the 7 cases in which mixed bile and pancreatic juice did not produce severe changes in the perfused esophagus, either the tryptic activity was below normal, or the pH of the solution was not optimal for tryptic digestion.† In those perfusions carried out with sodium taurocholate or sodium glycocholate the entire wall of the esophagus was necrotic. Free fluid which had diffused through the esophageal wall was always present in the mediastinum. Human bile caused the same degree of change in the cats' esophagus as dog bile unless the bile was obtained from a patient who had been on T-tube drainage for a long period of time, thus depleting the bile salts in the bile. Four experiments with such a bile failed to produce esophagitis in a single instance. Microscopically the esophagi showing the most severe changes stained poorly with H & E. There was marked edema of the esophageal wall and poor cellular detail. Erosions of the mucous membrane were pres-

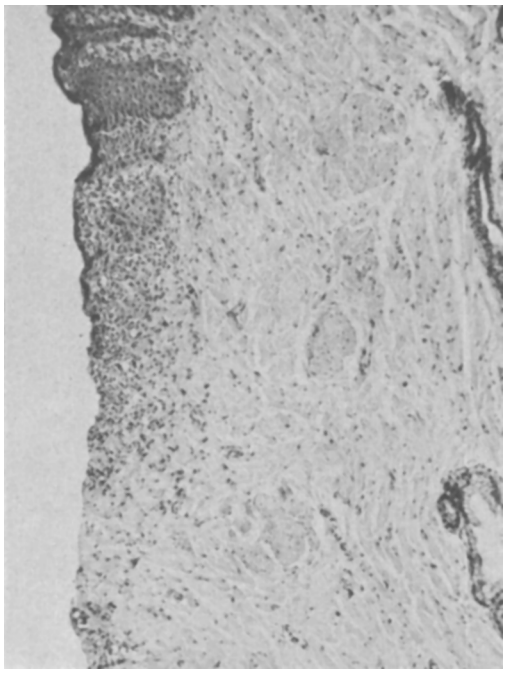

FIG. 2. Photomicrograph of an esophageal erosion caused by bile and pancreatic juice. Note that the lesion is shallow not extending beneath the muscularis mucosae.

† 0.2 cc of 1:10 dilution of test solution required to liquify 2 cc of gelatin substrate compared to the normal of 1.0 cc of a 1:100 solution. pH of test solutions ranged from 7.05 to 7.85. Optimal pH for tryptic digestion is 8-9.

TABLE II. Production of Esophagitis in Dogs.

Procedure	Total dogs	Esoph-agitis	No esoph-agitis
1. Bile and pancreatic juice diverted into esophagus	6	6	0
2. Bile diverted into esophagus	6	6	0
3. Pancreatic juice diverted into esophagus	6	6	0
4. Resection of acid secreting portion of stomach with diversion of bile and pancreatic juice into esophagus	4	4	0
5. Total gastrectomy with esophago-duodenostomy (regurgitation of bile and pancreatic juice)	7	5	2*
6. Excision of acid secreting portion of stomach; antral-esophageal anastomosis; extramucosal pyloroplasty	6	0	6
7. Succus entericus diverted into esophagus	5	0	5

* Bile duct occluded in one case not developing esophagitis.

ent with inflammatory cell infiltration of the submucosa.

B. Dogs. Bile, pancreatic juice, and mixtures of the two caused chronic lesions remarkably similar to each other when diverted into the esophagus of living dogs over periods of one to 3 months. At the time of esophagoscopy, as early as 8 days after the original operation, bleeding erosions were seen in the esophagus, and the mucosa was very easily traumatized. In these dogs there was a concurrent development of a severe anemia, either hypochromic or normochromic in nature, accompanied by positive benzidine and guaiac tests on the stools. The hemoglobin dropped to an average value of 9.5 g in the course of 4 to 8 weeks. The lowest value reached was 6.3 g, and in 4 dogs values between 7.0 and 8.0 g were observed. In order to keep these latter dogs alive, multiple transfusions were given. The erosions occurred over wide areas of the esophagus, most abundantly in the middle third, and often corresponded to the longitudinal folds of the mucous membrane (Fig. 1). Microscopically (Fig. 2) the lesions did not extend below the muscularis mucosae except in 2 instances when definite ulcers were present. Again, intestinal juice alone did not cause any changes nor was anemia observed.

It was also found that there was enough regurgitation of bile and pancreatic juice when an end to end esophago-duodenostomy was done to cause esophagitis in 5 out of 7 dogs. This was not true when the antrum remained as a reservoir even when an extramucosal pyloroplasty was done. When the entire acid secreting portion of the stomach was excised in addition to diverting all the bile and pancreatic juice into the esophagus, the development of esophagitis and anemia was observed consistently (Table II, item 4). In fact, the esophagitis and the anemia developing under these circumstances were comparable in every way to that observed when the stomach was intact. This finding rules out the regurgitation of acid gastric juice as being a factor in the development of the esophagitis. These results are summarized in Table II.

Discussion. The ability of bile and pancreatic juice to cause erosions of the esophagus has been established, and it has been shown that there is enough regurgitation of these juices after total gastrectomy and subsequent duodeno-esophagostomy in the dog to produce esophagitis. These observations confirm the suggestion that, when a total gastrectomy is done in man, a technic should be employed that precludes the regurgitation of the contents of the duodenal loop into the esophagus. Utilization of the Roux Y-plasty should be the best means to avoid this occurrence. In 2 dogs, erosions and hemorrhagic areas in the stomach, as well as esophagitis, were observed when the bile alone was diverted into the esophagus. These observations suggest the possibility that occult bleeding following gastric resection for duodenal ulcer in man may have its origin in the partial regurgitation of bile and pancreatic juice into the stomach through the gastrojejunostomy stoma. That esophagitis, of whatever origin in man, may be the source of some occult anemias appears likely.

Conclusions. (1) Digestion and destruction

of the living esophageal mucosa in cats and dogs can be accomplished by bile, pancreatic juice, and mixtures of the two. (2) Bleeding from esophageal erosions attending the complete diversion of bile and pancreatic juice into the esophagus in the dog causes a severe secondary anemia. (3) The development of the esophagitis and anemia in the dog is not altered by total excision of the acid secreting portion of the stomach.

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Effect of Inhaled Cigarette Smoke on Production of Peptic Ulcer in the Dog.* (18951)

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The effect of tobacco smoking on the etiology and course of peptic ulceration in man remains obscure. There is no reliable evidence that tobacco smoking causes peptic ulceration either experimentally or clinically. Barnett(1) failed to find a significantly greater proportion of smokers in 500 cases of peptic ulcer and gastric neurosis than in the general population. Gray(2) found 20% of ulcer patients failed to improve on medical management until tobacco was withdrawn. Batterman and Ehrenfeld(3) reported medical failures in 53.2% of habitual smokers and in 15% of non-smokers. Of the smokers who stopped of their own accord all responded satisfactorily to therapy; however when smoking was resumed, 85% had almost immediate recurrence of their disease. Trowell(4) found that men suffering from duodenal ulcer do not, on the average, smoke more tobacco than normal man but the practice of inhaling is twice as common in the ulcer group. Wolf and Wolff(5) reported no alteration in the motor and secretory activity of the stomach and color of the mucosa by pleasurable smoking. The purpose of this investigation was to study the effect of inhaled cigarette smoke on the production of experimental peptic ulceration in the intact dog.

Method of study. Healthy adult mongrel dogs were used in all experiments. All dogs had been under observation for at least one month and were free of distemper. Permanent lateral tracheostomies were prepared in the following manner: Through a vertical midline incision in the neck the trachea was dissected free and delivered into the wound. The strap muscles of the neck were sutured together beneath the trachea to form a sling-like support. The anterior one-third of 3 tracheal rings was excised, leaving the underlying tracheal mucous membrane intact. From a central point in this square window, radial incisions were made in the tracheal membrane to the 4 corners of the window. This resulted in 4 triangular flaps of tracheal mucosa. The edges of the skin incision were sutured to the edges of the tracheal window so that the sutures passed through the tracheal cartilage and the mucosal flaps were approximated to the raw skin edges. After a recovery period of at least one month, the tracheostomy was fitted with an ordinary T-tube and a small cigarette holder was adapted to the tube. Lighted cigarettes were placed in the holder and the dogs were allowed to inhale the smoke directly into the bronchial tree. Inhalation

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