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# Vagotomy Fails to Protect Against Histamine-Provoked Ulcer.*

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The occurrence of chronic peptic ulcer following bilateral vagotomy in rabbits has been observed by a number of investigators.[1] Recently, supradiaphragmatic vagus section has been used in the surgical treatment of gastroduodenal ulcer,[2] on the thesis that, the hypersecretion of night gastric juice common in ulcer patients is very largely neurogenic in origin. Gastrojejunostomy was used in some cases in addition to vagus section because of high grade pyloric stenosis. It is the purpose of this report to indicate our observations regarding vagus section in a few of the common laboratory animals (dog, cat and rabbit) and to note whether bilateral vagotomy or gastrojejunostomy and bilateral vagotomy will protect against the histamine-in-beeswax provoked ulcer.

*Method.* These experiments were carried out on 33 animals consisting of 13 dogs, 6 cats and 14 rabbits. Bilateral vagotomy was performed on these animals. After an average interval of 9 days in the dogs, 7 days in the cats and 8 days in the rabbits, the administration of the histamine-in-beeswax mixture prepared after the method of Code and Varco[3] was begun. Thirty milligrams of this mixture was injected intramuscularly each evening in the dog and rabbit, while 15 mg was injected in the cat. Following the injection the dogs' feed pans were removed and no more food was given until the following morning. Unless the animals succumbed from either aspiration pneumonia which often occurred after vagus section, or from ulcer provoked by the histamine implantation, they were sacrificed after varying periods of time to see if any ulcer were present at that time.

*Operative Procedure. Supradiaphragmatic Section.* This procedure was used on all the dogs (13), 2 cats and 9 rabbits. A long intercostal incision was made either in the fifth or sixth interspace. The muscles were then divided and retracted. Under positive pressure cyclopropane-oxygen anesthesia, the pleura was opened. The lungs immediately collapsed and controlled respiration was used during the operation. The left lung was retracted out of the field and the esophagus in the mediastinum became visible. The pleura over the lower esophagus was then opened and the organ mobilized. The left vagus and all visible and palpable fibers were then tied and sectioned accompanied by removal of a segment of 1 to 2 cm of the nerve. This procedure was repeated on the right vagus. In addition, in the dog, the proximal ends were sutured to the pleura lateral to the esophagus, as previously described by Dragstedt and Schafer.[2] This maneuver was not technically feasible in the rabbit and cat. The chest was then closed with interrupted cotton sutures.

*Infradiaphragmatic Section.* This procedure was used on 4 cats and 5 rabbits. These animals have a rather long infradiaphragmatic portion of esophagus and the vagi may be identified readily within the abdomen. Using a midline incision and pulling the stomach out on the abdominal wall and then downward and to the right, the infradiaphragmatic esophagus can be brought readily into view. The visible and palpable left and right vagi were then tied and sectioned and ½ to 1 cm of nerve removed. In addition, a circular area

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1 Beozell, J. M., and Ivy, A. C., *Arch. Path.*, 1936, **23**, 213.

2 Dragstedt, L. R., and Schafer, P. W., *Surgery*, 1945, **17**, 742.

3 Code, C. F., and Varco, R. L., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 475.

TABLE I.
Production of Ulcer in Dogs Following Supradiaphragmatic Vagotomy (30 mg Histamine-in-Beeswax Mixture Daily).

| Dog No. | Wt in lb | No. of injections | Results | Remarks | Wt of stomach, g |
|---|---|---|---|---|---|
| 419 | 38 | 45 | Antral ulcer; marked duodenitis; erosions in fundus | Sacrificed after 45 days; stomach dilated and atonic appearing | 129 |
| 420 | 40 | 45 | Marked duodenitis, erosions in antrum | Sacrificed after 45 days; stomach dilated and atonic appearing | 160 |
| 422 | 26 | 21 | Normal stomach and duodenum | Sacrificed after 45 days | 145 |
| 450 | 28 | 32 | Perforated ulcer lower esophagus | Died of perforation of esophageal ulcer into left thorax, stomach dilated | 95 |
| 453 | 36 | 40 | Erosions in antrum and duodenum | Sacrificed after 40 days, markedly dilated stomach | 163 |
| 454 | 28 | 12 | 3 duodenal ulcers, antral erosions | Died in 12 days, pneumonia probably caused by aspirated bile and gastric juice, bile present in bronchi | 155 |
| 457 | 26 | 8 | 4 duodenal ulcers, (2 perforating) | Pneumonia, dog vomiting, bile in bronchi | 138 |
| 458 | 30 | 40 | Normal stomach and duodenum | Tremendously dilated stomach | 185 |
| 459 | 36 | 14 | 3 small duodenal ulcers | Dead 2 weeks, empyema and pneumonia | 120 |

Number of dogs injected: 9.
Number of dogs with ulcer and/or erosion: 7.

TABLE II.
Production of Ulcer in Dogs Following Supradiaphragmatic Vagotomy and Gastrojejunostomy (30 mg Histamine-in-Beeswax Mixture Daily).

| Dog No. | Wt in lb | No. of injections | Results | Remarks | Wt of stomach, g |
|---|---|---|---|---|---|
| 428 | 31 | 4 | Normal stomach, duodenum and jejunum | Died of obstruction due to jejuno-jejunal intussusception | 165 |
| 430 | 41 | 17 | Perforated jejunal ulcer | Died of peritonitis | 140 |
| 434 | 39 | 45 | Large penetrating jejunal ulcer | Sacrificed 45 days, base of ulcer formed by adhesions and loop of bowel | 130 |
| 435 | 45 | 45 | Jejunitis, normal | Sacrificed 45 days, large atonic stomach | 136 |

No. of dogs injected: 4. No. of dogs with ulcer and/or erosion: 2.

TABLE III.
Production of Ulcer in Cat with Bilateral Vagotomy and Histamine-in-Beeswax (15 mg of Histamine-in-Beeswax Given Intramuscularly Once Daily).

| Cat No. | Wt in kg | No. of injections | Type of vagotomy | Results | Remarks | Wt of stomach, g |
|---|---|---|---|---|---|---|
| 1 | 2.5 | 10 | Infradiaphragmatic | Antral erosions | Sacrificed after last injection | 26.2 |
| 2 | 3 | 21 | " | Esophageal ulcers Antral ulcer | Severe vomiting during last few days | 19.2 |
| 3 | 2 | 8 | Supradiaphragmatic | Duodenal ulcer (perforated) | Received injections every other day | 24.3 |
| 4 | 3 | 21 | Infradiaphragmatic | 2 duodenal ulcers (1 perforated) | Sacrificed after 22 days | 24.5 |
| 5 | 1.5 | 31 | " | No ulcers | Sacrificed in 32 days | 16.1 |
| 6 | 2.5 | 31 | Supradiaphragmatic | 3 large duodenal ulcers | " | 20.5 |

No. of cats injected: 6.
No. of cats with ulcer and/or erosion: 5.

TABLE IV.
Production of Ulcer in Rabbit with Bilateral Vagotomy and Histamine-in-Beeswax (30 mg of Histamine-in-Beeswax Given Intramuscularly Once Daily).

| Rabbit No. | Size | No. of injections | Type of vagotomy | Results | Remarks | Wt of stomach, g |
|---|---|---|---|---|---|---|
| 4 | Adult | 7 | Infradiaphragmatic | Duodenal ulcer and bleeding antral ulcer | Sacrificed 8 days postoperatively | 26.5 |
| 5 | " | 21 | " | Bleeding duodenal ulcer | Empyema due to perforation of fundus ulcer into thorax | 24.2 |
| 9 | " | 10 | Supradiaphragmatic | Duodenal ulcer | Sacrificed in 11 days | 23.8 |
| 10 | " | 36 | " | No ulcer | Sacrificed in 37 days | 23.2 |
| 11 | " | 36 | " | " | " | 21.2 |
| 12 | " | 48 | " | " | Sacrificed in 48 days | 24.3 |
| 13 | " | 2 | " | Perforated duodenal ulcer | Postmortem 5 minutes after convulsion, blood in intestinal tract | 19.2 |
| 14* | " | 13 | Infradiaphragmatic | 2 esophageal ulcers | Sacrificed in 14 days | 23.5 |

* This rabbit received 15 mg of histamine-in-beeswax mixture for 8 days and 22½ mg for 5 days.
No. of rabbits injected: 8.
No. of rabbits with ulcer and/or erosion: 5.

TABLE V.
Production of Ulcer in Rabbit with Bilateral Vagotomy. (No Histamine).

| Rabbit No. | Size | Type of vagotomy | Results | Remarks | Wt of stomach, g |
|---|---|---|---|---|---|
| 1 | Adult | Supradiaphragmatic | Perforating fundus ulcer | Severe pylorospasm, sacrificed 5 days postoperatively | 20.1 |
| 2 | " | " | No ulcers | Sacrificed 29 days postoperatively | 21.7 |
| 3 | " | " | " | | |
| 6 | " | " | Large antral ulcer | Same 29 days | 22.2 |
| | | | | Same 36 days | 28 |
| 7 | " | Infradiaphragmatic | Bleeding cardiac erosions | Same 36 days, very edematous stomach | 32 |
| 8 | " | " | No ulcers | Sacrificed 13 days postoperatively | 21.5 |

on the wall of the esophagus was then denuded of peritoneum to insure destruction of all small vagus branches. The incision was then closed.

*Gastrojejunostomy.* The dogs were anesthetized with intravenous nembutal 15 mg per pound. Anesthesia was continued with intratracheal ether. Continuous gastric suction was applied during and immediately after surgery. Under aseptic conditions, a midline incision was made. The duodenum was transected and inverted immediately distal to the pyloric sphincter. One or 2 cm of stomach antrum including the pyloric sphincter was resected. Continuity of the intestinal tract was completed by aseptic gastrojejunostomy just beyond the ligament of Treitz.

Postoperatively, the dogs were fed parenterally for 72 hours with 10% glucose in saline solution containing some isotonic gelatine in normal saline. After 72 hours, water was allowed and the diet gradually increased thereafter until in one week the regular diet of tablescraps, horsemeat and kibbles was tolerated. This was reinforced with vitamins A, B, C and D. After an average interval of 92 days bilateral supradiaphragmatic vagotomy as described above was performed.

*Experiments.* Dogs. Thirteen dogs were used in this series. Bilateral supradiaphragmatic vagotomy was performed on these animals, 4 animals having had gastrojejunostomy performed previously. After a sufficient recovery period, the daily administration of the histamine-in-beeswax mixture was begun. One animal (dog 422) was sacrificed after 21 days as a test dog.

Cats. Six cats were used and all were sub-

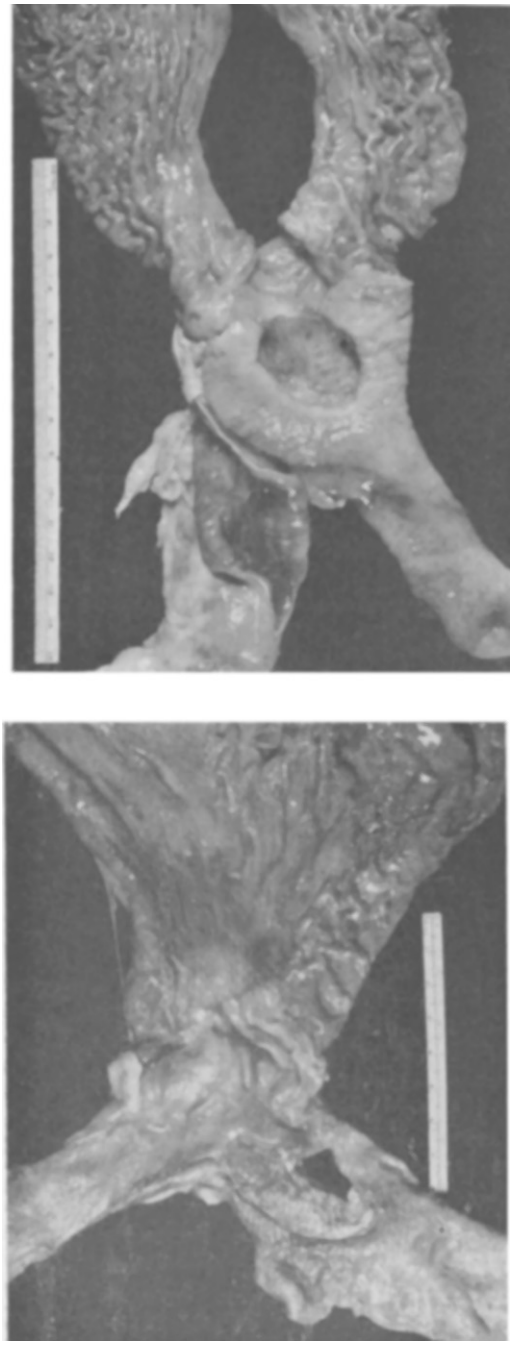

Fig. 1.

Stomachs of dogs with bilateral supradiaphragmatic vagotomy and gastrojejunostomy receiving histamine-in-beeswax. A. (Top) Dog 434 (left), large jejunal ulcer. B. (Bottom) Dog 430, (right), perforation of jejunum, died 17 days after commencement of histamine injections of peritonitis.

jected to bilateral vagus section and histamine-in-beeswax implantation. In addition, 3 control rabbits were subjected to a daily implantation of 30 mg histamine-in-beeswax mixture for 28 days.

Rabbits. Fourteen rabbits were used in this series. Six of these had bilateral vagotomy only, while 8 had both bilateral vagotomy and received histamine-in-beeswax in addition.

*Results.* The incidence of histamine-in-beeswax provoked ulcer or erosion (gastric and/or duodenal) following bilateral vagotomy and combined vagotomy and gastrojejunostomy procedure is shown in Tables I, II, III and IV. The occurrence of ulcer or erosion in the rabbit with bilateral vagus section alone is shown in Table V. In none of the control rabbits was ulcer or erosion observed.

*Comment.* It is worthwhile to comment on some of the postoperative complications attendant on bilateral vagus section. Marked atony and dilatation of the stomach was observed in most animals. The stomachs were not thickened on section but grossly they were very large. The presence of esophageal ulcer following histamine implantation was not an uncommon finding. Repeated vomiting was frequent in the dog and difficulty in swallowing was observed in many. This occurrence may explain the finding of esophageal ulcers and also the presence of bile in the bronchi of some of the dogs (Table I).

*Discussion.* These results indicate that bilateral vagus section or gastrojejunostomy and vagotomy do not protect against ulcer or erosion (gastric and/or duodenal) produced by chronic histamine stimulation. In addition, bilateral vagus section alone in the rabbit may produce ulcers. It has been suggested that this phenomenon may be due to trophic disturbances in the gastric wall brought about by vagotomy.[1] It has also been suggested that vagus fibers antagonize the vasoconstrictor action of the splanchnic nerves and when sectioned, the vasoconstrictor influence is unopposed.[4] It should be mentioned, however, that not only vagotomy, but also splanchnicectomy may be followed by gastric

[4] Alvarez, W. S., Hosoi, K., Overgard, A., and Ascanco, H., *Am. J. Physiol.*, 1929, **90**, 631.

ulcer in rabbits.[4] Recent evidence from this laboratory has shown that both vasoconstriction[5] and venous stasis[6] may aid and abet the ulcer diathesis by producing anoxic areas which then fail to resist the digestive action of the peptic mixture. Inasmuch as the effect of histamine is directly on the parietal cell, in the gastric tubule, the results of these experiments are not to be interpreted as a criticism of the application of vagotomy to the problem of ulcer in man.

*Conclusions.* 1. Bilateral vagotomy (infra- and supradiaphragmatic) failed to protect against ulcer or erosion (gastric and/or duodenal) produced by chronic histamine action in the dog, cat and rabbit.

[5] Baronofsky, I., and Wangensteen, O. H., *Bull. Am. Coll. Surg.*, 1945, **30**, 59.

[6] Baronofsky, I., and Wangensteen, O. H., PROC. SOC. EXP. BIOL. AND MED., 1945, **59**, 234.

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## Hemagglutination by Amniotic Fluid from Normal Embryonated Hen's Eggs.*

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During studies on the detection of influenza virus in throat washings[1] an agglutinin for guinea pig erythrocytes was noted in the amniotic fluid from certain inoculated eggs. Chicken red cells were not agglutinated by these fluids. This suggested that the fluids might contain the "O" form of influenza virus described by Burnet,[2] which grows only in the amniotic sac and which agglutinates guinea pig cells to higher titers than chicken cells. Subsequent study of amniotic fluid from uninoculated eggs, however, revealed that normal fluid also contained an agglutinin for guinea pig erythrocytes but not for chicken red cells. The phenomenon was unrelated to and independent of the presence of influenza virus.

The agglutinin was capable of clumping the erythrocytes of a wide variety of animals. It was present in the egg white of non-embryonated eggs and the albumin sac of embryonated eggs, gaining access to the amniotic sac after the establishment of the communication between it and the albumin sac which normally takes place between the 11th and 13th days of incubation.[3] It was associated with the globulin fraction of the egg white, was thermolabile, and was adsorbed to erythrocytes during agglutination. The characteristics of the hemagglutinin are described in this report.

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[1] Commission on Acute Respiratory Diseases, to be published.

[2] Burnet, F. M., and Bull, D. R., *Australian J. Exp. Biol. and Med. Sc.*, 1943, **21**, 55.

[3] Hirota, J., *J. Coll. Sc., Imp. Univ. Japan*, 1894, **6**, 339. Cited in Needham, J., *Chemical Embryology*, London, Cambridge University Press, 1931, vol. 2, p. 1100.