1.0 mμg angiotensin II generated/ml/3 hours. Four hours after nephrectomy, it was 1.3 ± 0.2 mμg. This suggests that the half-time of endogenous renin is similar to that of exogenous renin.

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The Effect of Unilateral Vagotomy on Gastric Secretion in the Pylorus Ligated Rat* (32679)

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Acute unilateral vagotomy was found by Shay *et al.* (1) to slightly reduce the rate of gastric secretion in the pylorus ligated rat, whereas bilateral vagotomy markedly reduced both the rate of secretion and the acid concentration. In contrast, in the dog, Sebus and Charbon (2) reported that the gastric secretory response to insulin hypoglycemia and to histamine was not altered by cutting 75% of the vagal fibers to the stomach. In man, it is generally believed that incomplete vagotomy is a cause of recurrent peptic ulceration, and is associated with a positive gastric secretory response to insulin hypoglycemia.

It is possible that the small reduction in the rate of secretion after acute unilateral vagotomy in the rat (1) was simply due to excessive handling of the glandular stomach and other abdominal organs at the time of nerve section. We have attempted to repeat the experiments of Shay *et al.*, performing unilateral vagotomy in some rats one week prior to pyloric ligation, and in others at the time of pyloric ligation.

Methods. Wistar rats, from 150–230 gm, were randomly allocated to four groups. Gastric secretion was collected by the method of Shay *et al.* (3). After fasting for 48 hours in individual cages with free access to water, pyloric ligation was performed under light ether anesthesia, and the stomach was washed out with 0.15 *M* NaCl through a soft rubber catheter passed orally. Four hours later the animals were reanesthetized with ether, and a

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TABLE I. Gastric Secretion in the Pylorus Ligated Rat after Unilateral or Bilateral Vagotomy.

Group	No. of animals	Mean rate of gastric secretion (ml per 100 gm body wt. per 4 hours)	Mean acid concentration (μeq/ml)	Mean acid output[a] (μeq per 100 gm body wt. per 4 hours)
Control (vagus intact)	13	2.55 ± 0.19[b]	99 ± 8	257 ± 24
Acute abdominal unilateral vagotomy	13	1.73 ± 0.19	83 ± 7	151 ± 27
Prior cervical unilateral vagotomy	13	2.29 ± 0.15	83 ± 5	195 ± 23
Acute bilateral abdominal vagotomy	13	0.98 ± 0.11	27 ± 2	28 ± 7

[a] Comparisons between acid output means (multiple range test). Control vs. acute abdominal unilateral vagotomy: difference 106 μeq, $p<.01$. Control vs. prior cervical unilateral vagotomy: difference 62 μeq, $p<.05$. Control vs. acute bilateral vagotomy: difference 229 μeq, $p<.01$. Acute abdominal unilateral vagotomy vs. prior cervical unilateral vagotomy: difference 44 μeq, $p>.05$. Acute abdominal unilateral vagotomy vs. acute bilateral vagotomy: difference 123 μeq, $p<.01$. Prior cervical unilateral vagotomy vs. acute bilateral vagotomy: difference 167 μeq, $p<.01$.

[b] Mean ± SE of the mean.

ligature placed at the cardia. Gastric contents were drained into graduated tubes, and centrifuged at 3000 rpm for 10 min. Any specimen containing more than 0.6 ml solids after centrifuging was discarded, as suggested by Shay *et al.* (3).

Each group initially consisted of 18 rats. One control group had only pyloric ligation. Another control group had acute bilateral vagotomy performed in the upper abdomen at the time of pyloric ligation. Unilateral vagotomy was performed in two test groups: in one group, either the anterior or posterior vagus was divided in the upper abdomen at the time of pyloric ligation. In the other group, either the right or left vagus was divided in the neck under ether anesthesia 7 days before pyloric ligation was performed. In the control group with intact vagal innervation, 5 samples were discarded as the solid content was in excess of 0.6 ml, leaving 13 specimens for analysis. In each of the other three groups, samples were collected until 13 acceptable specimens were available; any remaining animals were discarded without analysis of the gastric contents.

Gastric acid concentration was measured by titration with 0.1 *N* NaOH using phenolphthalein indicator. The results are given as the mean rate of secretion per 100 gm body weight per 4 hours, and as the mean acid output in μeq per 100 gm body weight per 4 hours. Duncan's multiple range test (4) was calculated for individual mean comparisons.

Results. Acute bilateral abdominal vagotomy caused a marked reduction in the rate of secretion of gastric juice, the acid concentration, and the acid output in 4 hours in the pylorus ligated rat (Table I). The acid output after unilateral vagotomy was significantly smaller than the acid output of the control rats, and significantly greater than the acid output of the group subjected to bilateral vagotomy: these differences were apparent whether unilateral vagotomy was performed in the neck 1 week prior to pyloric ligation, or in the abdomen at the time of pyloric ligation. There was no significant difference between the mean acid outputs of both unilateral vagotomy groups.

In the group subjected to unilateral cervical vagotomy, six rats had the left vagus divided, and the mean acid output of this subgroup was 178 μeq per 100 gm per 4 hours: seven had the right vagus divided, and their mean acid output was 210 μeq per 100 gm per 4 hours. In the group in which unilateral vagot-

omy was performed in the abdomen, seven rats had the posterior vagal trunk divided, and the mean acid output of this subgroup was 130 μeq per 100 gm per 4 hours: six had the anterior vagal trunk divided, and their mean acid output was 175 μeq per 100 gm per 4 hours.

Discussion. We have found that unilateral vagotomy significantly reduced the mean acid output in pylorus ligated rats (Table I). Shay *et al.* (1) reported that acute unilateral vagotomy reduced the rate of secretion of gastric juice in the pylorus ligated rat to 78% of control values: in our experiments, the mean rate of secretion of gastric juice in both unilateral vagotomy groups (taken together) was 79% of the control values. Shay *et al.* found no difference in the acid concentration after unilateral vagotomy: however, we found that unilateral vagotomy reduced the acid concentration to 84% of the control values (Table I). The mean rate of secretion of gastric juice and the mean acid concentration after bilateral vagotomy were similar in the two studies.

It is possible that the slight reduction in the rate of secretion of gastric juice described by Shay *et al.* after acute unilateral vagotomy may have been due merely to excessive handling of the glandular stomach and other abdominal organs at the time of nerve section. However, unilateral vagotomy in the neck 7 days before pyloric ligation also caused a significant reduction in acid output (Table I): this excludes the possibility that the difference in the acute experiments was due to trauma. Cervical unilateral vagotomy was chosen in order to leave the abdomen free of adhesions for pyloric ligation 1 week later.

Cannon and Rosenblueth (5) postulated that autonomic nerves might supply only certain "key" cells, and diffusion of transmitter substances from this region was able to influence more distant effectors. This theory implies that partial division of the nerve supply of a gland would have little if any influence on the amount of secretion produced by a standard nervous stimulus. In the salivary glands, electrical stimulation of the chorda appears to cause maximal rates of secretion (6): it seems probable that this form of excitation stimulates all of the secretory units of the gland. Hillarp (7) found that stimulation of the chorda after destruction of some of the parasympathetic fibers caused cytological signs of secretory activity in some acini, while neighboring acini seemed to be at rest. This was taken as evidence that diffusion of a chemical mediator from its site of liberation does not play a major role in the excitation of more remote glandular secretory units.

It has been suggested that the spontaneous secretion in the unanesthetized pylorus ligated rat is almost entirely due to vagal influences (1,8). The finding that unilateral vagotomy significantly reduces this spontaneous secretion argues against the diffusion theory of Cannon and Rosenblueth, and favors the view that individual vagal fibers supply separate "secretory units." As far as we are aware, this is the only experimental evidence that partial destruction of the parasympathetic nerve supply to a glandular organ will cause a significant reduction in its external secretion.

In the dog, Sebus and Charbon (2) claimed that the gastric secretory response to histamine and to insulin hypoglycemia was not altered by cutting 75% of the vagal fibers in the thorax. This may represent a species difference; however, at least one of their three dogs did have a smaller response to histamine after partial vagotomy. This study is also open to the criticism that gastric collections were made using an esophageal tube, and the authors themselves admitted that there was some doubt as to the adequacy of the collections.

Summary. Unilateral vagotomy reduced the spontaneous secretion of gastric juice in the pylorus ligated rat. The mean acid output after unilateral vagotomy was significantly smaller than the acid output in control rats, and significantly greater than the mean acid output after bilateral vagotomy. Similar differences were observed whether unilateral vagotomy was performed in the abdomen at the time of pyloric ligation, or in the neck 1 week prior to pyloric ligation.

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Scrapie in Mice: Ultrastructural Observations in the Cerebral Cortex (32680)

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Scrapie is a chronic, progressive, degenerative disease of the central nervous system occurring naturally in sheep and experimentally in goats, rats, hamsters, and mice. The remarkable stability of the scrapie agent in the presence of formalin (1) and heat (1) suggests that the scrapie agent may not be a conventional virus (2). Its resistance to inactivation by ultraviolet light of wavelength specifically absorbed by nucleic acids and its susceptibility to inactivation by electron irradiations are properties that suggest that the scrapie agent may not contain nucleic acid and that its molecular weight is likely to be no greater than 2.0×10^5 which means that its size is probably less than that of any known virus (3).

The work reported in this paper was undertaken to obtain by electron microscopy information of use in elucidating the brain pathology of experimentally induced scrapie in the mouse; in its course a number of previously undescribed structures were observed in the cerebral cortex of scrapie infected mice. It is the purpose of this report to describe these structures.

Materials and Methods. Scrapie agent. The strain of scrapie used was that described by Pattison and Chandler who have reported in detail its isolation from sheep (1) and its adaptation to growth in goats (2) and mice (1).

Source of study materials. At the National Institutes of Health the scrapie agent was readily transmitted to and maintained in Swiss-NIH mice by brain to brain passage, following procedures already described (4). In the present work saline suspensions were prepared from the infected brains of Swiss-NIH mice at the third and eight passage level and these were inoculated intracerebrally into weanling, specific-pathogen-free, Balb-C mice of a breed developed by L. T. Fitzwater, Animal Production Unit, NIH. Six months post-inoculation when the test mice were in the advanced stages of clinical scrapie their brains were harvested for study. Control material consisted of the brains of specific-pathogen-free mice that were inoculated 6 months previously with a suspension of brain tissue from normal Swiss-NIH mice.

Microscopic techniques. One hemisphere of each brain harvested from scrapie and control mice was frozen at —60°C for future use; the other hemisphere from each mouse was fixed in 3% glutaraldehyde. Small cubes of cerebral cortex were cut from the fixed hemisphere, washed in Millonig's phosphate buffer at pH 7.3 (5), postfixed in 2% osmic acid and embedded in Epon. Thick sections were stained with toluidine blue for examination with the light microscope. Thin sections were mounted on carbon coated grids, stained with uranyl acetate and lead citrate and examined in a Siemens Elmiskop 1A.

Tests for contaminating viruses. A search