A STUDY OF THE GASTRIC ULCERS FOLLOWING REMOVAL OF THE ADRENALS.

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PLATES 27 AND 28.

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It was noted at autopsy that animals dying after the removal of both adrenals showed acute ulceration of the gastric mucosa in a large number of cases.

Cioffi and Pende made this same observation, but Gibelli[1] was the first to give it special attention. The most extensive investigation of the subject was made by Finzi[2] in a study of the gastric mucosa of rabbits and dogs after removal of the adrenals. He found in the gastric mucosa marked circulatory changes consisting of edema, hemorrhage, necrosis, and ulceration. In the few instances in which there was a tendency to heal, the slight healing process involved only the connective tissue, never the epithelium. He found edema and hemorrhagic points in the stomach as early as one hour after extirpation of the adrenals. Dissection of the capsule of the adrenal, leaving the gland intact, did not produce ulceration. The removal of one adrenal in a rabbit produced slight and transient circulatory changes in the gastric mucosa. Animals which were given adrenalin after removal of the adrenals had normal gastric mucosa. In five cases of gastric or duodenal ulcer in man he found microscopic changes in the adrenals, consisting of thickening of the capsule, nodular hypertrophy, fatty degeneration, great congestion, and multiple hemorrhage. He believes that adrenal insufficiency may be a factor in the etiology of gastric ulcer.

Durante[3] investigated the effects of section of the splanchnic nerves on the

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[1] Gibelli, C., La funzione delle capsule surrenali in rapporto col processo di riparazione delle fratture e coll' eziologia dell'ulcera gastrica, *Pathologica*, 1909, i, 131.

[2] Finzi, O., Über Veränderungen der Magenschleimhaut bei Tieren nach Nebennierenextirpation und über experimentell erzeugte Magengeschwüre, *Virchows Arch. f. path. Anat.*, 1913, ccxiv, 413.

[3] Durante, L., Contributo alla fisiopatologia del nervo splancnico, *Pathologica*, 1912–13, v, 631.

gastric mucosa and adrenals in dogs and rabbits. He found that section of all three splanchnics on either side produced no change except congestion in the adrenals; section of the major splanchnic affected the gastric mucosa very slightly; section of either the median or minor splanchnic on either side always produced necrosis and ulceration of the gastric mucosa. The ulcers produced by section of the nerves on the right always healed rapidly and the spleen remained normal; section of the nerves on the left produced changes in the spleen and ulcers in the stomach which tended to become chronic. He attributed the formation of ulcers after adrenalectomy to incidental injury of the minor splanchnic nerves which are buried in the posterior leaf of the adrenal.

Since this investigation was undertaken two articles bearing on the subject have appeared. Elliott[4] notes the frequent occurrence of gastric ulcer on removal of the adrenals in cats, and cites it as proof of the full digestive power of the gastric juice. He refers to the work of Finzi and concludes with the statement that gastric ulcer is not found in Addison's disease.

Friedman[5] investigated the effect on the gastric and duodenal mucosa of removal of the adrenals and one-side thyroidectomy in dogs and rabbits. He considered gastric lesions possibly dependent upon adrenal insufficiency as well as upon an excess of thyroid; duodenal lesions upon hypofunction as well as upon excess of adrenalin; coexistent gastric and duodenal lesions upon alternating conditions of hypo- and hyperfunction of the adrenals. He relies upon the pluriglandular hypothesis of an antagonistic action between the adrenals and the thyroid to explain the formation of gastric and duodenal ulcers and erosions after interference with these glands.

Dogs and cats were used in my investigation.[6] As no lesion of the gastric mucosa was found at autopsy in a series of more than 200 practically normal animals, it would seem that spontaneous ulcers are not common in these animals. Their occurrence after adrenalectomy was studied in the following series of experiments.

Experiment 1.—In four dogs the adrenals were removed at one operation and the animals kept under an anesthetic until death occurred, two or three hours

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[4] Elliott, T. R., Some Results of Excision of the Adrenal Glands, *Jour. Physiol.*, 1915, xlix, 38.

[5] Friedman, G. A., The Influence of Removal of the Adrenals and One-Sided Thyroidectomy upon the Gastric and Duodenal Mucosa; the Experimental Production of Lesions, Erosions, and Acute Ulcers, *Jour. Med. Research*, 1915, xxxii, 287.

[6] These ulcers have also been noted in gophers dying from adrenal insufficiency, and in one case of Addison's disease.

after the removal of the last gland. In these experiments the mucosa of the stomach and duodenum was found to be normal.

Experiment 2.—In twelve dogs the adrenals were removed at two operations. When the second gland was removed the dogs were kept under ether until death occurred, which was from two to eight hours after operation. In none of these animals were gastric or duodenal lesions noted.

Experiment 3.—Forty dogs and six cats were subjected to the removal of one adrenal, usually the right, and killed at periods varying from 5 hours to 235 days after operation. In this series of animals no lesion of the gastric or duodenal mucosa was found except in one dog. This animal died from an unknown cause 4 months after removal of the right adrenal; several acute ulcers and one chronic ulcer were found in the stomach and one acute ulcer in the duodenum.

Experiment 4.—Of sixty dogs and five cats in which both adrenals were removed at the same operation or at different operations, forty animals showed lesions of the stomach, five of these ulcers of both stomach and duodenum. Of the twenty-five animals in which ulcers were not found, only four died an uncomplicated death from adrenal insufficiency; the remaining twenty-one animals were either subjected to other experiments which may have interfered with the formation of ulcers or they died before the ulcer could form.

It is seen that lesions of the gastric and duodenal mucosa did not occur in adrenalectomized animals subject to continuous etherization and were infrequent in animals subjected to the removal of only one adrenal; but lesions in the stomach and duodenum occurred in about 90 per cent of the animals dying with the characteristic symptoms of adrenal insufficiency after removal of both glands. This last fact appears significant in the study of the general causative factors of acute gastric ulcers.

It has been impossible to determine definitely the time necessary for the formation of the ulcers or how soon after complete adrenalectomy they begin to form. In only one of the animals examined within ten hours after removal of both adrenals were any changes noted in the gastric mucosa. In this instance there were several hemorrhagic areas which were possibly the beginning of ulcers. In one animal dying twenty-two hours after extirpation of both glands well formed ulcers were present. In animals examined when muscular weakness was first in evidence, beginning ulceration was noted. No changes in the gastric mucosa were found before decrease in blood pressure took place. It would appear that ulcer formation begins before the onset of the characteristic symptoms of adrenal insuffi-

ciency which progress until the death of the animal, and that only a few hours are necessary for their production.

The lesions found in the gastric mucosa after death from adrenal insufficiency consist of two main types: one is a wide-spread, superficial erosion; the other is a true, punched-out ulcer formation.

The gastric erosions practically always occurred in the fundic division, and in most cases the pyloric mucosa appeared normal. They appeared to begin in and spread along the rugæ, thus producing an irregular appearance. Only the surface of the mucosa was affected, the loss of epithelium never extending to the submucosa. The denuded surface was hemorrhagic in appearance, and the fluid in the stomach was usually blood-stained. This condition developed mainly in those animals in which there was a prolonged moribund condition following the development of muscular weakness.

The gastric ulcers were round or oval in shape and varied in size from 2 mm. to 2 cm. in diameter. They were usually multiple, but a few stomachs contained only one ulcer. Their position varied; they were found in the fundic and pyloric regions on both the greater and lesser curvatures. Usually they occurred in the prepyloric division. Beginning ulcers appeared as small hemorrhagic areas; when fully formed, however, they penetrated to the muscularis mucosa with a complete loss of epithelium. The walls were smooth, giving the characteristic punched-out appearance. A small blood vessel was usually found in the base of the ulcer. When the autopsy was performed immediately after death, in many instances the vessels were bleeding. In the pyloric region the blood gave the ulcer a black appearance, while in the fundus it often remained bright red at the site of the ulcer. In most instances the ulcers constituted the only pathologic change in the mucosa, while in other specimens the mucosa was injected throughout (Figs. 1 and 2).

The duodenal mucosa was usually congested in the adrenalectomized animals. In five experiments there were definite ulcers. These duodenal ulcers occurred just distal to the pyloric ring and appeared like cauterized areas about 1.5 cm. in diameter. They were deeper at the center than at the edges. They penetrated to the muscularis mucosa at the center. They never showed evidence of hemorrhage (Fig. 2).

Microscopically, the picture of the ulcer varies slightly; usually, however, they are cone-shaped with the base of the cone at the surface and the apex at the muscularis mucosa. The edges of the ulcer are clean, although occasionally there may be some cellular débris and blood at the base (Fig. 3). None but the earliest signs of healing have ever been observed.

The loss of tissue appears to begin at the surface. The gland cells disappear first, allowing the supporting tissue to fall together. In some cases the ulcer has not extended to the muscularis mucosa. In these ulcers the gland cells below the base may appear perfectly normal. Hemorrhage seems to be of early occurrence in the formation of the ulcer. In practically all ulcers the blood vessels in the vicinity are congested. The special stains for mucin demonstrate the fact that this substance is usually absent near the ulcers (Fig. 4). The glands in the vicinity of the ulcer may appear normal, but do not contain mucin. The zymogen content of all the cells is decreased, but no more so in the cells around the ulcer than elsewhere.

It has been suggested that the regurgitation of pancreatic secretion is the cause of gastric ulcers and that tryptic ulcer would be a more exact term than peptic ulcer. That the pancreatic secretion is not necessary for the formation of these ulcers was proved by a series of five experiments in which the pancreatic ducts were either doubly ligated and sectioned, or a pancreatic fistula was made before the removal of the last adrenal. In these animals no pancreatic secretion could reach the gastro-intestinal tract, yet many characteristic gastric ulcers were found after death.

It has been demonstrated that bile in association with a strongly acid gastric juice has an erosive action on the gastric mucosa.[7] That the bile might be of importance in the production of these ulcers seemed possible because of the fact that the fluid found in the stomach was usually bile-stained. In one animal the common bile duct was transplanted to the skin, thus making it impossible for any bile to enter the stomach. After complete recovery from the operation,

[7] Smith, G. M., An Experimental Study of the Relation of Bile to Ulceration of the Mucous Membrane of the Stomach, *Jour. Med. Research*, 1914, xxx, 147.

the adrenals were removed. Well formed ulcers were found at autopsy.

The gastric content was always acid in the adrenalectomized animals. In order to determine the part the acid played in the production of the ulcers, an attempt was made to neutralize it during the moribund period. To accomplish this sodium bicarbonate was administered about every four hours, either in solution by stomach tube or in capsules. Of course, it was impossible to be sure that the gastric contents were always kept neutralized, but certainly in most instances no great excess of acidity developed. In a series of ten experiments in which sodium bicarbonate was administered after the removal of the last adrenal, ulcers were found in one animal only. In this experiment it is possible that the bicarbonate was not given frequently enough to prevent the development of acidity. This result would tend to show, as has been demonstrated in regard to the formation of other acute ulcers, that acid is a factor in their production.[8]

In a series of ten experiments a gastro-enterostomy was performed during the interval between the removal of the adrenals. In only four of these animals were ulcers found. It is possible to explain this result as due to a reflux of the alkaline intestinal secretion and the bile.

SUMMARY.

Acute ulcers of the gastric mucosa are found in a large percentage of dogs and cats dying after adrenalectomy. These ulcers seem to develop during the moribund period. They are apparently peptic ulcers forming at the site of local hemorrhages in the gastric mucosa. They are true acute ulcers, usually penetrating to the muscularis mucosa with a total loss of epithelium. They develop in the absence of pancreatic secretion and bile. However, they appear to develop only in an acid medium.

[8] Bolton, C., Ulcer of the Stomach, London, 1913, 59.

FIG. 1.

FIG. 2.

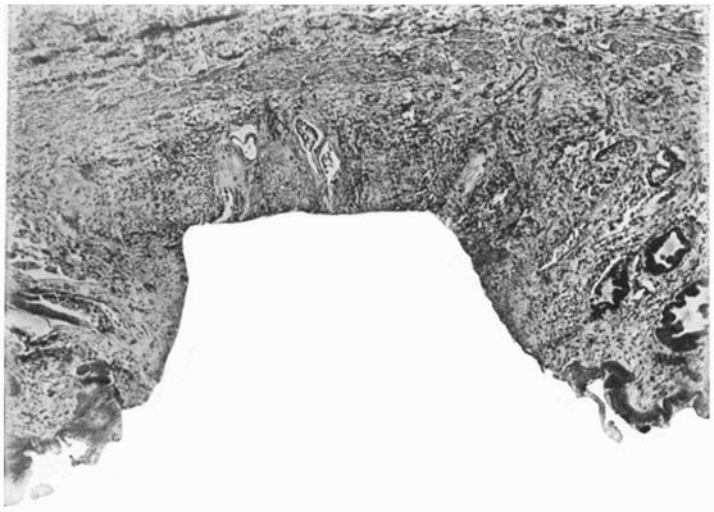

FIG. 3.

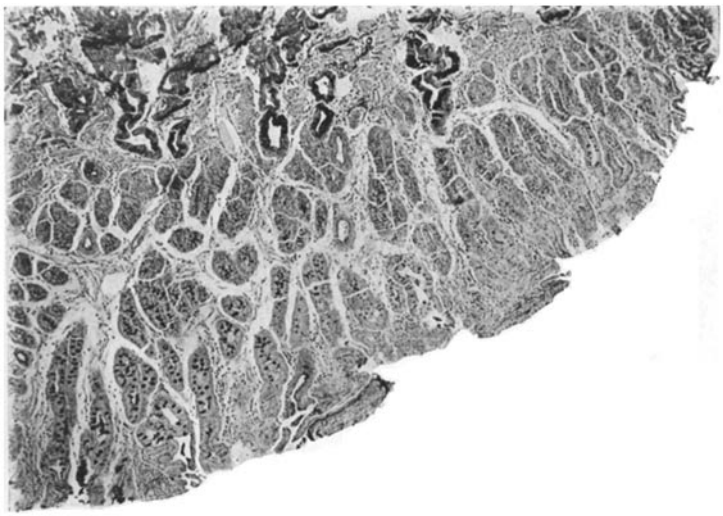

FIG. 4.

(Mann: Gastric Ulcers.)

EXPLANATION OF PLATES.

PLATE 27.

FIG. 1 Gastric mucosa of a dog, showing multiple acute ulcers.

FIG. 2. Pyloric and duodenal mucosa, showing multiple acute ulcers.

PLATE 28.

FIG. 3. The center of a gastric ulcer, showing the clean edges and base.

FIG. 4. The edge of a duodenal ulcer, showing the loss of goblet cells (the dark stained cells) in the vicinity of the ulcer.