GASTRIC ULCERS IN RABBITS FOLLOWING RESECTION OF THE PNEUMOGASTRIC NERVES BELOW THE DIAPHRAGM.

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PLATE XI.

The experiments reported in this paper were suggested by an article published by Van Yzeren,[1] one of Talma's assistants, in 1901. Van Yzeren cut both vagi in twenty rabbits below the diaphragm and observed the development in ten of chronic ulcers, usually single, in the pyloric region of the stomach. His results appear more remarkable still when we take into account that of the ten rabbits without ulcers, seven lived five days and less (five only one day), whereas the first ulcer was found in a rabbit that had lived seven days. Of the rabbits examined later, three only did not show ulcers (one examined on the ninth, one on the tenth, and one on the forty-seventh day). The last rabbit was examined 289 days after the operation and showed an ulcer still present.

Van Yzeren was preceded in this work by two Italian investigators: Lorenzi and Saitta. In 1893, Lorenzi[2] reported that after resection of the vagi either at the neck or below the diaphragm in rabbits, hemorrhages were frequently observed in the mucous membrane of the stomach and in some cases from these, when the animals survived longer than twenty-four hours, hemorrhagic erosions developed. In 1900, Saitta[3] performed

[1] Van Yzeren, "Die Pathogenesis des chronischen Magengeschwürs," *Zeitsch. f. klin. Med.*, 1901, xliii, 181.

[2] Lorenzi, "L'influenza del sistema nervoso nella patogenesi dell' ulcera dello stomaco," *Rassegna di Sc. med.*, 1893.

[3] Saitta, "Contributo alla patogenesi dell' ulcera gastrica," *Gaz. degli Ospedali Milano*, 1900, xxi, 599.

bilateral vagotomy at the neck in sixteen rabbits, in which he treated as well as possible the resulting disturbances in respiration and heart action. Three of the rabbits died on the second day and showed normal stomachs, three died on the eighth to the tenth day and showed black ecchymotic spots in the mucosa, and the remaining four died on the fifteenth to the twentieth day, showing hemorrhages and erosions in the mucous membrane. In four rabbits that had been operated upon in a similar manner and had been given 3 per cent. hydrochloric acid solution by mouth, he found multiple ulcers.

In 1901, dalla Vedova [4] studied the influence of disturbances in innervation on the gastric mucous membrane of dogs. His experiments were not confined to the vagus nerve, but included the ganglia cœliaca and the left splanchnicus magnus. The nerves were either resected, or alcohol, which, according to him, has the same effect, was injected into them. In six instances he resected the dorsal branch of the vagus below the diaphragm or injected alcohol into it without result. In twelve animals he succeeded in removing the left or both ganglia cœliaca. Positive results were observed in five of the latter. He removed the left splanchnicus magnus successfully in ten dogs, with nine positive results. These animals lived from one to sixty days. In all the positive cases but two he found hemorrhages and hemorrhagic erosions, and in the two remaining he found larger hemorrhagic, funnel-shaped ulcers. The last occurred after resection of the ganglion cœliacum, the animal living three days, and after injection of alcohol into the left splanchnicus magnus, the dog surviving the operation eighteen days.

The most recent paper on the subject, which is quite full, was published by Donati.[5] Donati resected both vagi below the diaphragm in nine dogs and eleven rabbits, extirpated the plexus cœliacus in eleven dogs and five rabbits, and removed both of these at the same time in one dog. He also resected

[4] dalla Vedova, "Ricerche spirimentale sulla patogenesi dell' ulcera gastrica," *Arch. ed atti della soc. ital. di chir.*, 1901; *Archiv für Verdauungskrankh.*, 1902.

[5] *Archiv für klin. Chirurgie*, 1904, lxxiii, 908.

A short notice of the same work also appeared in the *Zentralblatt für Chirurgie*, 1904, xxxi, 346.

both vagi at the neck in six dogs, but these animals lived only four to five days. He resected one vagus at the neck in three dogs, the animals being killed between the thirtieth and sixty-fifth day; and in another dog he resected one vagus at the neck and later the other one, the animal surviving eighty-one days. In all these experiments the results were entirely negative. Donati gives a very complete review of the literature, inclusive of the experiments made by physiologists in order to ascertain the function of the gastric nerves, and points out that as far as lesions in the mucous membrane of the stomach are concerned the results have been most contradictory. From his review of the literature and from the result of his own experiments he comes to the conclusion that very probably the hemorrhages, erosions, and even ulcers, described by other observers, were entirely accidental, and that disturbances in innervation have no effect whatever upon the mucous membrane of the stomach.

In spite of Donati's work it seems difficult to understand how the results of Van Yzeren could be due entirely to accident. Even granted that hemorrhages and erosions are comparatively frequently found accidentally in the gastric mucosa of animals, especially in rabbits, and my own experience leads me to be certain of this, still typical chronic ulcers have, at least as far as I am aware, never been described as occurring spontaneously in these animals. This point seems all the more important as rabbits are so very commonly used for experimental purposes and on that account carefully examined. In the opinion that chronic ulcers of the stomach do not occur spontaneously in rabbits I am confirmed by observations made on a considerable number of controls in the course of my own experiments on this subject.

In these experiments I have confined myself entirely to rabbits and have always resected both vagi below the diaphragm. The operation is easily performed. The animals are anæsthetized with ether, an incision is made along the free margin of the ribs on the left side, and the stomach is exposed and drawn downwards. After tearing through a thin peritoneal fold, which runs from the stomach to one of the lobes of the liver, the lower end

of the œsophagus, which passes quite a distance through the diaphragm, is exposed; the nerves can then be easily found and a piece of about ½ cm. in length resected without producing any hemorrhage to speak of. If the anæsthetic is carefully given the animals recover very rapidly from the operation, and with fairly careful antiseptic precautions one should not lose any of them by accident. The animals operated on were examined at varying intervals. They do not as a rule show any bad symptoms as a result of the operation and remain in a fairly good state of nutrition. In a few instances only was a considerable degree of emaciation noticed, although not necessarily in those animals in which gastric ulcers developed. A careful examination of the site of operation was made in all cases in order to determine whether both vagi had been cut and, also, in order to exclude any complications resulting from a possible infection at the point of operation. In the first days following the operation one notices very little reaction. Later, a small amount of dense cicatricial tissue develops in which the cut ends of the vagi are embedded and which, on the other side, adheres to the cardiac end of the lesser curvature of the stomach. The amount of cicatricial tissue found was no greater in the animals developing ulcers than in the ones which gave negative results. I have never been able to find any macroscopic evidence of regeneration of the nerves.

Thirty rabbits were operated upon in this way and the results are shown in Table I, page 185. The transverse fold mentioned is one which is plainly seen when one examines *in situ* the interior of the stomach of a rabbit through an incision along the greater curvature. Several smaller and one large transverse fold are then noticed at the lesser curvature between cardia and pylorus and a little nearer to the pylorus. This fold becomes narrower and lower on both sides and disappears before it has reached the greater curvature.

There were then six positive results in thirty experiments, or, if we exclude those animals examined before the twenty-fourth day, at which day the first ulcer was found, six positive results in eighteen experiments were obtained. It is at once apparent

that in my series the ulcers developed much less regularly than in Van Yzeren's series. Whenever they were found, however, they corresponded very closely to Van Yzeren's description. They were undoubtedly chronic ulcers, as was shown by the marked induration at the base; they appeared of round or oval form, with sharp edges and smooth bottom. All the ulcers which I ob-

TABLE I.

No. of Rabbits Examined.	Day after Operation.	Result.
1	3d	Negative.
2	5th	"
2	7th	"
1	8th	"
1	10th	"
1	11th	"
2	15th	"
1	17th	"
2	18th	"
1	24th	Transverse oval chronic ulcer about 8 x 10 mm. on summit of fold. Sharp edges, smooth bottom.
1	26th	Negative.
1	34th	Small chronic ulcer on fold.
1	39th	Negative.
1	42d	"
1	45th	"
3	50th	In one, small chronic ulcer 2 mm. from pylorus.
1	60th	Chronic oval ulcer 7 x 9 mm. on summit of fold; sharp edges.
2	64th	In one, nearly healed ulcer with much induration on summit of fold.
4	71st	Negative.
1	88th	Small chronic ulcer on anterior wall in pyloric region, but near fundus.

NOTE.—Of thirty rabbits operated upon and examined six showed ulcers of the stomach. No ulcer found earlier than 24th day. Eighteen rabbits examined after 24th day; hence ulcers developed in 33 per cent. of these rabbits.

tained were single, while Van Yzeren observed several instances in which they were multiple. Since Van Yzeren neglected to give any pictures of the ulcers I have photographed one of the larger ones, which is shown in natural size in Fig. 1. This photograph also shows well the relation of the ulcer to the transverse fold. Sections were made of two of the larger ulcers. The ulceration extended, in one case, into the muscle, and in the

other, of which a microphotograph is given (Fig. 2), through the muscle into the subperitoneal tissue. In both ulcers there was a considerable development of cicatricial tissue at the base, which was covered with a thin layer of necrotic material including fibrin, blood, remnants of food, etc. The mucous membrane at the edge, as may be seen in the microphotograph, may show a considerable hypertrophy and project over the ulcer. The larger arteries and veins near the ulcer were carefully examined in numerous sections; they were found to be entirely normal.

During the course of the experiments I have examined the stomachs of a large number of normal rabbits. I have several times found small hemorrhages, and in one case I found a hemorrhagic erosion with complete destruction of the mucous membrane over an area of about 2 mm. in the center, on the summit of the above described fold, but the process was evidently quite recent. At the bottom of the defect there was a narrow zone of necrosis and a few leucocytes could be seen in the tissues beneath, but no other reaction was visible. I have examined certainly as many normal rabbits as operated ones. All our rabbits are kept together in a large rabbit pen, to which the animals operated on were returned after they had sufficiently recovered from the operation. Hence all the rabbits eat the same food and are otherwise kept under identical conditions. The rabbits used in the experiments were taken from the same lots as were those which were examined without operation.

It could therefore hardly be a matter of chance that the chronic ulcers were found only in the animals operated upon which survived the operation twenty-four days or longer. I have already mentioned that if chronic ulcers in rabbits occur at all spontaneously, they must be very rare indeed. I believe, therefore, that in spite of Donati's eleven negative experiments we are safe in concluding that resections of both vagi below the diaphragm in rabbits may be followed by the formation of peculiar chronic ulcers beginning in the mucous membrane of the stomach, but that this result is not either constant or remarkably frequent.

The question arises as to what relation exists between the

section of the nerves and the production of the ulcers. We should enquire, naturally, first of all, of the function which the vagus nerve exerts upon the stomach and what the disturbances of this viscus are after the nerve is cut.

It can hardly be doubted that the motions of the stomach are to a certain extent under the influence of the vagus nerve. That this is true can be plainly seen upon stimulating electrically or otherwise the two vagi below the diaphragm. The result is a strong contraction of the muscle of the stomach, which seems to be similar to the normal contractions, but more vigorous; and, if the stimulation is not so strong as to produce a tonic contraction, the contractions are repeated more frequently. It is also claimed by some that the vagus nerve contains inhibitory fibres. If, on the other hand, the nerve is cut, it has been found that the movements of the stomach are retarded, but that otherwise they continue unchanged. In my experiments I noticed in the first weeks a marked dilatation of the stomach. The normal capacity of an ordinary rabbit's stomach is about 100 to 120 c.c. The capacity was increased often to 180 c.c. or more. At the same time in these instances it was noticeable that the elastic properties of the gastric wall were unaltered. With the increase in contents there was a marked rise in pressure within. The dilated stomachs therefore felt very hard to the touch, and on that account could be easily palpated through the abdominal wall in the living animal. The operated animals seem somehow to overload their stomachs. I believe that it is this condition that misled Van Yzeren and led him to assume that tonic cramps of the muscle occurred after the resection; at least I have never seen any evidence of the occurrence of such cramps. In all my instances the hardness of the organ was plainly accounted for by overfilling. This disturbance of motion seems in course of time to be compensated, for in all the animals examined late the stomach had returned to its normal size and the tension of the wall had become normal.

On the whole, the vagus seems to have very little influence upon the secretion of gastric juice. Pawlow, it is true, has demonstrated that the central reflex for the secretion of the gastric juice

passes through the vagus, because in his dogs the secretion of gastric juice ordinarily taking place when they see tempting food is missing when the vagus is cut. But our rabbits seem to have done well in the absence of this central reflex. Direct stimulation of the nerves below the diaphragm is followed by the appearance of considerable gastric juice upon the mucous membrane, which phenomenon can be repeated several times after the secretion has been wiped away. Still, it is of course impossible to decide whether an actual secretion takes place as a result of the stimulation or whether preformed gastric juice is simply squeezed out of the mucous membrane by the contraction of the muscular elements in it. In any case the proper secretion of gastric juice does not seem to have been disturbed materially in our rabbits by the section of the vagi. The contents of the stomach of the operated animals had absolutely normal appearances and the chemical examination did not reveal any constant changes. The result of the chemical examinations made by Töpfer's method in several rabbits is given in Table II. The figures represent the number of cubic centimeters of decinormal solution of sodium hydroxide necessary to neutralize 100 c.c. of gastric juice. The latter was obtained by adding an equal volume of distilled water to the gastric contents and filtering. The figures obtained with the filtrate were doubled. The method may not be entirely accurate, but it gives comparable values. It was of course impossible to obtain the gastric juice always at the same stage of digestion, which probably accounts for the rather wide discrepancies in the figures.

Another possibility that suggests itself as an explanation of the formation of the ulcers after resection of the vagi is the disturbance of those protective mechanisms which seem to exist in the gastric and intestinal mucous membranes in order to prevent undue injury to them from their contents. These mechanisms have been described by Exner [6] and by Müller.[7] These

[6] Exner, "Wie schützt sich der Verdauungstract vor Verletzungen," *Arch. f. Phys.*, 1902, lxxxix, 253.

[7] Müller, "Beitrag zur Kenntnis von den Schutzeinrichtungen des Darmtractes," etc., *Arch. f. Phys.*, 1904, cii, 206.

authors found that mechanical irritation of the mucous membrane of the intestines and of the stomach in dogs and cats produces, first, an anæmia at the point of irritation, which is followed by a small dimple resulting from the contraction of the muscularis mucosa at the spot. Exner had already noticed that the same phenomenon occurs in the intestines of animals shortly after death, or even when pieces of intestine have been cut out. Müller sometimes observed a disappearance of the phenomenon in the stomach of cats after resection of the vagi below the diaphragm, but at other times there was no change.[8]

TABLE II.

	Total Acidity.	Free HCl.	Loosely Comb. HCl.	Organic Acids and Acid Salts.
Normal rabbit	124	96	4	24
" "	88	76	8	42
" "	148	128	16	4
" "	132	132		
Rabbit 5 days after operation	92	72	4	16
" 11 " " "	96	48	16	32
" 42 " " "	100	80		20
" 50 " " "	112	72	8	32
" 50 " " "	132	104	16	12
" 50 " " " with small ulcer in pyloric region	88	48	8	32

I was led to make similar experiments upon the mucous membrane of the stomach of rabbits by the fact that the disturbances arising from section of the vagus at the neck are commonly ascribed partly to interference with normal reflexes, such as, for instance, the laryngeal reflex. The gastric mucous membrane of rabbits also responds to mechanical irritation in a definite and similar manner to that described for cats and dogs by

[8] Both Exner and Müller describe these phenomena as due to reflex action. I have purposely avoided this term in the above description, because in spite of their arguments to the contrary it does not seem definitely settled whether they could not be the result of direct stimulation of the muscular elements in the mucous membrane. It is probably the chief if not the only function of the muscularis mucosæ to draw the mucous membrane away from points of mechanical irritation.

Exner and Müller. It is interesting to note that the response of the mucous membrane is much more prompt and marked in the region of the lesser curvature, which is the usual site of the ulcers. This difference is so distinct, that while in the fundus one notices hardly any effect on pricking or touching the mucous membrane with a blunt instrument, the anæmia and the motion in the mucous membrane are quite evident under similar conditions at the lesser curvature. As a result of the first tests in which I irritated the mucous membrane chemically, a form of irritation to which it reacts much less promptly, I had the impression that cutting of the vagus interfered with or completely abolished the reaction; but this opinion has not been borne out by my later experiments with mechanical irritation. Indeed it would seem as if the reaction was sometimes even more marked after the vagi were cut. The reaction also persists for a time after section of the vagi. Animals were examined at varying intervals after operation and no change in the reaction was noticed. In one case I had the opportunity of testing for the reaction in a stomach that was the seat of a chronic ulcer. No reaction could be elicited in the immediate neighborhood of the ulcer, but this was probably due to the immobilization of the mucous membrane by the chronic inflammatory process. A little farther away the reaction was weak, but undoubtedly present. It cannot therefore very well be any interference with this protective reaction that causes the ulcerations.

I believe that originally the ulcers are traumatic in origin, due to the presence of hard, more or less pointed, substances in the food. This explanation would account for their occasional or more frequent presence, depending on accidental circumstances, and serve to harmonize my results with those of Van Yzeren. Their position on the summit of a projecting fold is suggestive also of this mode of origin. The hemorrhages and erosions observed in the stomach of normal rabbits are also probably due to the same cause. It seems, however, very difficult to explain why the ordinary defects produced in this way heal rapidly, while after section of the vagi a tendency to development of chronic ulcers exists.

Van Yzeren bases his explanation of the origin of the ulcers on the occurrence of cramps in the muscle, which he claims to have observed. He believes that the cramps interfere with the blood supply of the mucous membrane and produce an anæmic necrosis at the point where the ulcer is to develop. He found confirmation of this theory in certain experiments in which he not only cut the vagi, but also made deep incisions into the muscle from the outside, or performed gastroenterostomy. If the latter operations, designed to relieve the cramps, were added, no ulcers developed. Quite apart from the fact that it seems more than doubtful whether such cramps actually occur, it is not easy to understand how they could produce a localized anæmic necrosis; and, even assuming that they do so, it still remains to be explained how such an obstacle to the usual rapid healing of defects could operate. Since the ulcers do not occur as regularly as Van Yzeren believed, his comparatively few experiments designed to prevent the occurrence of them by the above described means are, to my mind, hardly conclusive.

One could imagine that traumatism is more apt to occur when the stomach is overfilled and very tense, as is the case in the first week after vagotomy; and that the increased pressure of the contents might also stand in the way of a proper healing of any defect produced in this fashion. Unfortunately, for this supposition, the motor conditions seem to return to the normal after a little while. Still, it is a well-known fact that after chronic ulcerative processes have once been started, healing may be retarded though the pathological conditions that caused the ulceration be removed.

It seems necessary to discuss one other possibility, namely, that the ulcers belong to the so-called tropho-neurotic lesions; that is, that through the resection of the nerves trophic influences are removed which are necessary to preserve the normal resistance of the mucous membrane. I believe this explanation should be accepted only after all other possible explanations have been exhausted, and yet from the data on hand, it has certainly to be considered. There is something mysterious about the assumption of such tropho-neurotic influences that is

somewhat contrary to our ordinary modes of reasoning; and still it cannot be denied that certain well-known facts could hardly be explained otherwise than on the basis of some such hypothesis.

I believe then that my experiments have shown that in rabbits there is some relation between the resection of the vagi below the diaphragm and the occurrence of chronic ulcers of the stomach. The experiments, I am sorry to say, have not shed much further light on the question of what this relation is. I also believe that it would be entirely premature to make use of these experiments in the explanation of peptic ulcer in man, although I acknowledge that the resemblance between the two processes is striking.

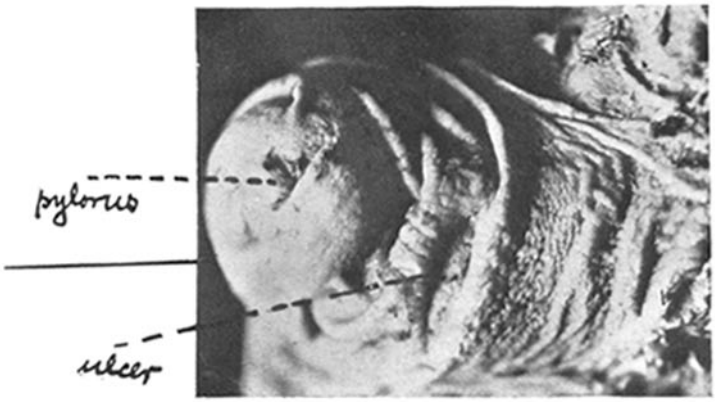

FIG. 1

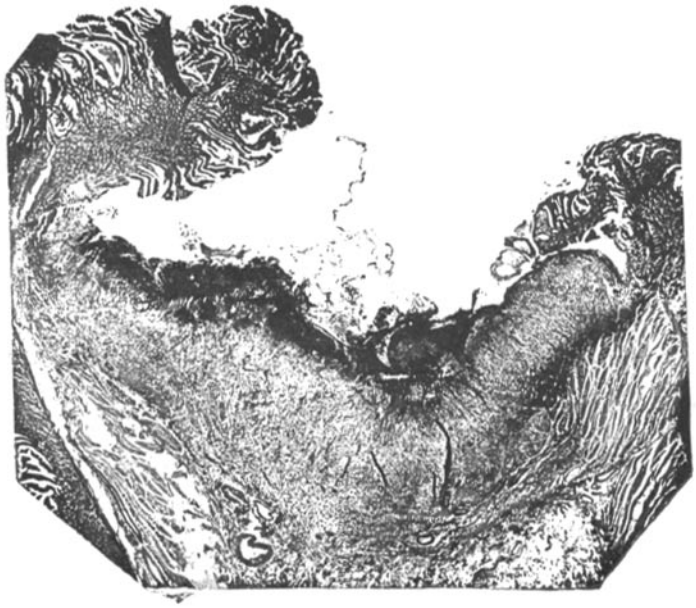

FIG. 2