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ABOLITION OF PYLORIC SPASM BY ORALLY ADMINISTERED PROCAINE SOLUTIONS

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In the course of an investigation into the mechanism of the pyloric reflex it was found that "novocain" (procaine B.P.) given by mouth paralysed the pyloric sphincter. The technique used was the usual method of screening during and after the administration of barium sulphate suspension ("barium meal"). The type of pyloric activity observed in the large majority of healthy individuals, and therefore accepted as normal, was a slow "worm-like" opening and closure.

The investigation arose out of the observation that often when the first portion of contrast medium reached the pylorus the sphincter was patent and it passed into the duodenum without delay. Whether initially open or closed, the sphincter subsequently acted as follows: (1) it remained open; (2) it contracted and relaxed rhythmically in what has been called the "worm-like" movement; or (3) it closed abruptly—that is, went into spasm after the initial filling of the duodenal cap, and either remained closed or reopened only after prolonged deep massage of the epigastrium.

As the subsequent behaviour of the pyloric sphincter seemed to be unrelated to its initial state, the problem to be solved was, What determines whether the sphincter is originally open or closed?

We have observed that if the volume of contrast medium first entering the stomach is large enough to distend the pyloric antrum quickly (which can be achieved by inducing the patient to drink the suspension rapidly) the sphincter is nearly always found to be open. If, however, the barium suspension has been taken some time before screening (whatever the speed of swallowing), or if the contrast material is drunk slowly during the screening, the pylorus is nearly always found closed. The essential point of the latter circumstances seems to be the gradual filling of the pyloric antrum.

These facts suggested that the pylorus of an empty normal stomach under physiological conditions is open. Therefore, a series of cases was investigated in which it might reasonably have been suspected that the pyloric

sphincter was at first closed—for example, gastric ulcers, gastro-enteritis, carcinoma ventriculi, etc. It was noted that, even in some of these cases, if the contrast material was consumed rapidly it found the sphincter open. In these cases, after some barium had passed through, the sphincter went into spasm. From observations on several hundred cases over the course of almost four years it was deduced that under physiological conditions, in an empty stomach, the pyloric sphincter is open; it is closed only by some effect upon it of material passing from the stomach—whether nutrient or radio-opaque in character.

Holzknacht and Jonas (1909) have shown that in the empty stomach, although the walls of the pylorus are close together, the sphincter has a very low tonicity, so that material which does not act as a stimulus—for example, isotonic fluid at 37° C.—can pass it without hindrance. Hot or cold, hypertonic or solid materials cause a closure in most cases. This is in accordance with the observations mentioned, because the fine suspension of barium at body temperature, reaching the antrum at once, does not initiate this slow reflex mechanism, which is, however, put into action by the contrast material when this is drunk slowly.

Klee (1920) and Kestner (1924) found that the tonicity of the pylorus alters rhythmically and depends always on that of the stomach. Wheelon and Thomas (1921, 1922) proved with balloon experiments that the tonicity of the pylorus corresponds to that of the antrum. This was confirmed by Bárony and Hortobágyi (1924). The present work seems to confirm the suggestions that contrast material causing tonus in the stomach acts also as a stimulus to the closing of the pylorus.

However, there are indications that it is not only the tonicity of the stomach that determines the behaviour of the pylorus. As is known from the experiments of Cannon (1911), significant changes may occur in the tonicity without affecting a constantly closed or constantly open pylorus. These observations suggest that the pyloric reflex mechanism has extragastric components as well.

Probably the most important of the extragastric components is the autonomic nervous system. The vagus fibres end in the cells of the Auerbach plexus. However, consistent results are not obtained from their stimulation. McCrea and M'Swiny (1928) found that in the hypermotile stomach it initiates movements. It is generally accepted that the sympathetic nervous system relaxes and the vagus closes the pylorus as suggested by Thomas, Crider, and Morgan (1934).

Beattie and Sheehan (1934) stated that in the tuber cinereum there is a stimulating centre, while in the back of the hypothalamus an inhibiting centre is found. However, after total denervation of the stomach there occurs only a short pause in its movements. The vagus-compression experiments of Danielopolu *et al.* (1924) demonstrate mixed stimuli because the vagus itself is a mixed nerve.

The theory of the role of acid and base in the pyloric reflex is to-day regarded as doubtful. Van Liere and Sleeth (1940) stated that increase of acidity increased motility, but this was denied by other authors (McClure *et al.*, 1920; Baird, Campbell, and Hern, 1924; Bárony and Egan, 1925; McCann, 1929).

Experimental Findings

Statistical data were collected from barium-meal cases examined during the period 1940-6. The series consisted only of "normal" cases in which the barium-meal examination was done chiefly as a control and in which no specific

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alimentary symptoms were present. The following results were obtained in 1,000 cases of this type :

Pylorus opening with difficulty or remaining closed	177
Hyperchlorhydria	142 (80.2%)
Normal	17 (9.6%)
Hypochlorhydria or achlorhydria	18 (10.2%)
Pylorus opening normally	801
Hyperchlorhydria	551 (68.8%)
Normal	100 (12.5%)
Hypochlorhydria or achlorhydria	150 (18.7%)
Pylorus opening with abnormal ease	22
Hyperchlorhydria	15 (68.2%)
Normal	2 (9.1%)
Hypochlorhydria or achlorhydria	5 (22.7%)

These results would suggest that the degree of acidity of the gastric contents plays no part in the reflex mechanism of the pylorus, although the number of cases tested may be too small to be entirely convincing.

Other workers have investigated this particular problem, but it was thought advisable to repeat some of their experiments. The procedure of Bársony and Egan (1925) was therefore carried out on 50 normal cases, of which 25 showed an easily and 25 a difficult opening pylorus. A duodenal tube was passed into the stomach. The contrast medium was swallowed five minutes later and the opening of the pylorus was observed. Now 20 ml. of N/10 HCl or NaHCO₃, depending on whether the pylorus opened with difficulty or with ease, was injected through the tube and the patient again drank some of the contrast medium. (By examination on the previous day and on the days following the experiment it was ascertained that the pyloric reflex reacted in a constant manner.)

The results obtained corresponded with those previously published (McClure *et al.*, 1920; Baird *et al.*, 1924; Bársony and Egan, 1925; McCann, 1929). An easily opening pylorus still opened with ease after injection of acid, and the pylorus that opened with difficulty acted similarly after injection of the alkali. Again the suggestion is that the degree of acidity of the stomach contents does not influence the reflex mechanism of the pylorus.

In order to find supporting evidence the experiment on these 50 patients was repeated, but this time the duodenal tube was passed into the duodenal cap, under the same conditions as before. The result remained unchanged: injection of acid or alkali into the duodenal cap, and within physiological limits, did not disturb the reflex mechanism.

Mechanical Irritation

The moving of the duodenal tube caused pharyngeal irritation and nausea, which were associated with an abrupt closure of the pylorus. On the other hand, the rubbing of the wall of the pylorus by the oliva caused a distinct worm-like movement of the muscle. This worm-like closure of the pylorus could be produced by other mechanical means—injecting fluid into the pylorus under considerable pressure, or slight distension of a balloon placed in the pylorus. (Stronger inflation of the balloon caused spasm by the smooth-muscle reflex.)

Finally, a continuous irritation of the pharynx for five to ten minutes produced a hypersensitive state of the pylorus during which very slight stimuli, such as gentle pressure on the abdominal wall, were followed by a steady closure. But even under these conditions the closure was a transitory spasm and not the physiological worm-like movement.

It therefore seems that the primary stimulus for the physiological closure of the pylorus is a local irritation of its wall. A similar result is obtained with the contrast medium: a little of the medium passes first without hindrance through the pylorus; during its passage it acts as a mechanical stimulus and the medium that follows finds

the pylorus closed. If the patients began to swallow the medium before the screening was done the pylorus was invariably found closed—that is, the first part of the barium meal passing through had started the reflex mechanism. Local stimulus does not necessarily mean local reflex mechanism. The autonomic nervous system undoubtedly plays its part, but the literary data are rather contradictory. It is most generally accepted that closure of the pylorus is brought about by a vagus effect (McCrea and M'Swiny, 1928; Thomas *et al.*, 1934), but Elliott (1905) believed it to be a sympathetic effect, which, however, was contradicted by Scholtz (1928) and Thomas *et al.* (1934).

Effect of Adrenaline, Atropine, and Papaverine

The effect of adrenaline and atropine was investigated in 75 cases—25 with a normally opening pylorus, 25 with a pylorus opening with ease, and 25 with a pylorus opening with difficulty. The results indicated that the role of these drugs in the physiological movements of the pylorus is only secondary. Injection of adrenaline, 1 mg. subcutaneously, always resulted, after 10 to 30 minutes, in a difficult opening, but it never caused normal closure and never pyloric spasm. There is no doubt that sympathetic stimuli inhibit the emptying of the stomach by inhibiting the opening of the pylorus, as was described in the alarm reaction of Cannon.

Atropine, 0.5 mg. intravenously, has practically no effect on the normal pylorus, but results in an atonic stomach; two hours after the injection and the swallowing of the barium meal half of the contrast material is still found in the stomach. However, in the case of a spastic pylorus the atropine usually causes opening of the sphincter in five to ten minutes, but as the stomach again loses its tone the emptying is nevertheless protracted. It was mentioned earlier that vagus stimulation produced by irritation of the pharynx resulted in a strong spastic closure of the pylorus.

These results show that pyloric closure may result from mechanism depending on the autonomic nervous system, but in the physiological movements of the muscle this system plays a secondary part. The experiments of Aldehoff and Mering (1899) confirm this contention: they found that even after extirpation of the coeliac ganglion the pyloric reflex remains unchanged, and they therefore believed it to be an intramural reflex.

Papaverine gave better results (Erdélyi, 1934). In 25 cases with a spastic pylorus the sphincter was usually opened by this drug, but large doses were sometimes necessary (0.2 to 0.3 g. intramuscularly), and unpleasant subjective symptoms occurred, such as blushing, vertigo, palpitations, and nearly always drowsiness. As mentioned by Erdélyi, the drug takes effect only after an hour, and the area of injection may remain painful for one to two days. As atony of the stomach is produced the residuum increases in cases of organic stenosis of the pylorus.

Papaverine has very little effect on the normal pylorus. As the drug acts directly on smooth muscle these observations would indicate that the muscle itself also plays only a secondary part in the pyloric reflex mechanism.

Part Played by the Local Nervous System

Finally, the role of the local nervous system was investigated. To inhibit its action the following simple method was used. The patient while in a sitting position drank 100 ml. of a 1% procaine solution, and was instructed to take four to five minutes over it. The movements of the pylorus were observed 5, 10, or 15 minutes later. The dose of procaine (1 g.) is about ten times the oral dose

usually recommended in textbooks of pharmacology. However, the same dose, and even a higher one, has been given hypodermically without serious ill-effect. As the literature did not indicate more rapid absorption of procaine by the oral than by the subcutaneous route (rather the reverse), the dosage was cautiously increased until an optimum level was reached. This dose (100 ml. of 1% procaine) has been given to a large number of patients, and to many twice in the day, without any side-effects.

It is generally accepted that procaine has very little effect on the intact mucous membranes. It seemed, however, to be the least toxic of the local analgesics, and was thus the first to be tried.

The results surpassed all expectations. In more than 150 normal cases nearly complete paralysis of the pylorus was produced in 10 minutes. The pylorus became perfectly atonic and the contrast material passed through the stomach without the slightest hindrance. At the same time the movements of the stomach remained normal, the autonomy being unaltered.

Procaine given orally also prevented reflex response to local irritation as produced by rubbing with the oliva, forceful injection through the tube, or slight inflation of the balloon. In more than 100 cases in which previous x-ray examination showed a spastic pylorus and slow emptying of the stomach with a constant residue, oral procaine caused relaxation of the sphincter, except in those cases in which the pyloric canal was obstructed by carcinoma or by scarring from an old ulcer.

In 11 cases of chronic vomiting in association with gastric ulcer this method prevented vomiting by paralyzing the pylorus. In five cases of cancer of the stomach, in which the patient could not retain food, procaine given orally enabled the patient to be fed naturally, and, by correcting the hypochloræmia and malnutrition, to be made fit for operation.

Discussion

It seems probable that the primary control of physiological movements of the pylorus rests with the local nervous system and that this system can be paralysed by procaine. Earlier observations that substances coating the wall, such as protein solutions or oil, will also relax the pylorus support this suggestion (Boldireff, 1904; Tabora and Dietlen, 1911; Kirschner and Mangold, 1911).

In our experience even the most difficult and hopeless-looking spastic pylorus would relax with this simple therapeutic agent. It had no side-effects. The relaxation lasted for two to three hours, and the treatment could be repeated twice daily for several days without causing discomfort.

Pyloric obstruction, which had not shown real improvement after atropine or papaverine, responded to procaine. Free passage lasting for hours resulted, and vomiting stopped. Its main use was naturally in functional spasm, but even organic obstruction caused by carcinoma or chronic ulcer would often improve to such an extent that a patient who seemed to be a serious surgical risk after days of starvation and continuous vomiting, with hypochloræmia and dehydration, could be changed to a lesser problem for the surgeon.

Summary

When the stomach is empty the pyloric valve is physiologically open. Closure of the valve is caused by the passage through it of the first small amount of stomach content.

The injection of 20-40 ml. of acid or base in physiological concentration into the stomach or duodenum through a duodenal tube does not influence the mechanism of the pyloric valve.

Stimulation of the sympathetic nervous system (adrenaline) or of the vagus (pharyngeal irritation) causes a sudden but short closure. This is not identical with the physiological reflex mechanism, but is part of the integrative functions of the autonomic nervous system (alarm reaction, vomiting, etc.).

The physiological worm-like movement can be produced by slight local stimulation of the wall of the duodenum (movement of an oliva, slight balloon inflation).

It is suggested that in the closure of the normal pylorus stimulation of the local nervous system plays the primary part. The irritation is mostly mechanical. This suggestion seems to be proved by oral administration of procaine, when the resulting paralysis of the local nerve endings opens a spastic pylorus with much greater regularity than atropine or papaverine.

Procaine was given orally to several hundred cases with spastic pylori, always with striking results. This simple method keeps the pylorus open for some hours, has no side-effects, and can be repeated daily twice for several days (50-100 ml. of 1% solution twice daily). It is recommended as a simple therapeutic procedure, useful in functionally spastic pylorus and as a preparation for surgical intervention in cases of organic pyloric obstruction.

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Dr. Marcolino Gomez Candau, of Rio de Janeiro, Brazil, has been appointed to the post of Director, Division of Organization of Public Health Services, in the World Health Organization. He will direct the W.H.O. programmes for developing public health administration, health demonstration areas, environmental sanitation, health education of the public, and nursing services. Dr. Candau, who was born in Rio de Janeiro in 1911, completed his medical studies at the School of Medicine of the State of Rio de Janeiro and at the School of Hygiene and Public Health of Johns Hopkins University, Baltimore. He was previously superintendent of the Serviço Especial de Saúde Pública, a co-operative public health programme of the Brazilian Government and the Institute of Inter-American Affairs. Dr. Victor Sutter, of San Salvador, has been put in charge of the Division of Communicable Diseases Services, and will direct the W.H.O. campaigns against malaria, tuberculosis, and venereal diseases, as well as programmes against plague, typhus, relapsing fever, bilharziasis, and other communicable diseases. He obtained his medical degree at the Universidad Nacional of San Salvador, and specialized in public health administration at Johns Hopkins University. At one time Dr. Sutter was chief field medical officer for Unrra in China.