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Tetraethylammonium chloride in the treatment of peptic ulcer

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TETRAETHYLAMMONIUM CHLORIDE IN THE TREATMENT OF PEPTIC ULCER

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INTRODUCTION

Tetraethylammonium chloride (Etamon, Parke, Davis & Co.) is a compound closely related in chemical structure to acetylcholine. Tetraethylammonium salts have been employed successfully, both therapeutically and diagnostically, in a number of peripheral vascular diseases and other conditions involving vascular dysfunction. The drug has accomplished this by partially blocking, in man, the transmission of both sympathetic (thoracicolumbar) and parasympathetic (craniosacral) nerve motor impulses through autonomic ganglia. This same pharmacologic action produces the following physiologic effects on the stomach (1): "decrease in gastric acidity; decrease in gastric motility, inhibition of increased gastric acidity normally following insulin-induced hypoglycemia. These effects follow bilateral vagotomy." It is for this reason that Lyons, Moe et al of the University of Michigan Medical School, Acheson of Harvard Medical School, Binter and Thomas of Wichita, Kansas, and others have been interested in studying the experimental and clinical action of this drug in the treatment of peptic ulcer. This paper, then, is a review of these findings.

It would be difficult, if not impossible, to discuss adequately the pharmacologic action of the tetraethylammonium ion on gastric behavior and its subsequent value in treating peptic ulcer without first outlining briefly the pertinent points concerning the anatomy and physiology of the stomach, the etiology and pathology of ulcer formation, and the rationale of past and current ulcer therapy. For this reason, a detailed discussion of tetraethylammonium chloride will be preceded by the above mentioned topics.

For the sake of brevity, the symbol, "TA", will be used to represent the tetraethylammonium ion, and "TAC" will signify the salt, tetraethylammonium chloride.

ANATOMY AND PHYSIOLOGY

In discussing the anatomy and physiology of the stomach and duodenum, we are chiefly concerned in this paper with the innervation (both motor and sensory) and the motor and secretory activities of this portion of the digestive tract. This review is drawn mainly from standard texts on physiology (2,3).

The extrensic innervation of the stomach is through both the right and left vagus nerves and the sympathetic. Both vagus fibers enter into the formation of the

esophageal plexus. From the latter, two trunks, each of which contains fibers from the right and the left vagus, emerge. The anterior vagal trunk supplies the anterior surface of the stomach and the posterior trunk, the posterior surface. The pyloris and first part of the duodenum receive a special branch which arises from the anterior trunk. The medullated preganglionic fibers of the parasympathetics (vagus) reach the intestinal walls through the mesentery. In the connective tissue between the two layers of muscle, these fibers are associated with groups of parasympathetic ganglion cells to form the plexus myentericus or plexus of Auerbach. The processes of the ganglion cells interlace, forming a large part of the plexus. The axons are grouped together in small bundles of non-medullated fibers, which pass, together with the sympathetic fibers, into the muscular coats, where they form intricate plexuses, from which are given off club-shpaed terminals to the smooth muscle cells. From Auerbach's plexus fibers pass to the submucosa, where they form a similar but finer meshed and more delicate plexus also associated with other groups of parasympathetic ganglion cells, the plexus of Meissner. From Meissner's plexus delicate fibrils pass to their terminations in submucosa,

muscularis mucosae, and mucous membrane.

The non-medullated sympathetic fibers arise as preganglionic trunks of the level thoracic five through thoracic eleven. The postganglionic fibers of the sympathetic (cell stations in celiac ganglion) end by arborizations around the muscle cells.

The effects of experimental stimulation of either of these nerves cannot always be predicted. Vagal stimulation may cause either augmentation or inhibition of gastric motility. Inconstant effects are also caused by sympathetic stimulation. The result depends upon several conditions, e.g., the frequency and strength of stimulus, the level of the tone of the muscle at the time and the activity of the peristaltic movements. Generally speaking, when the tone of the gastric muscle is high, inhibitory effects are produced by vagal stimulation, whereas in states of low tonus a motor effect is obtained. The sympathetic is generally considered to be inhibitor to the pyloric sphincter and the vagus excitatory, but an opposite effect may be obtained from either nerve, the tonus level at the time appearing to be a determining factor. Though variability in response is quite evidently a characteristic of the gastric nerve, their functions can be summarized in the statement that the vagus is

predominately motor and stimulates motility of and secretion within the stomach: the sympathetic is predominantly inhibitory in the above respect.

After section of both sets of extrinsic nerves to the stomach, motility is abolished but returns after a time, the movements then being governed by the intrinsic nervous mechanisms. The evidence for the liberation of acetylcholine by vagal stimulation is quite conclusive. The gastric vagi also contain afferent fibers. Section of one vagus and stimulation of its central end is followed by movements of the stomach.

Afferent pain stimuli are not transmitted by vagal afferent fibers but are carried by fibers coursing with the splanchnic sympathetics. These have no ganglionic synapse and are anatomically and pharmacologically similar to peripheral sensory nerves. Perception of gastroduodenal pain is lost when splanchnic sympathetics are severed, or when spinal anesthesia reaches the level of T 6. (4). Such perception of pain is not lost when the vagus is cut.

There is not general agreement as to the exact mechanism whereby the apin is produced in peptic ulcer. Palmer (2, p.447) is a proponent of the concept that the pain of the peptic ulcer arises directly from

irritation of the ulcer base by gastric acid. The more generally held opinion is that ulcer pain arises more immediately from disturbances of the motor mechanism of the stomach and duodenum (2, p.447). The well known relief of ulcer discomfort when gastric acidity is reduced leaves no doubt as to the existance of some relationship between acid, ulcer, and pain. This relationship need not depend upon primary nerve end-organ reception of pain stimulus within the ulcer. That it does not would seem to follow the observation of Smith et al (4) of active peptic ulcer immediately following vagotomy with splanchnic sympathetics intact. They found that introduction of excess acid into the stomach in such instances failed to induce pain.

Binter. Thomas, and Rankin (5) offer an hypothesis which they feel reconciles divergent views. They believe that chemical irritation of an ulcer crater produces local reflex spasm provimate to the site of ulceration. Motility or hyper-motility of the stomach forces gastric contents against the partial obstruction of the site of the spasm. Distention of the viscus (ordinarily the distal part of the stomach) proximal to the obstruction affords the immediate origin of pain. This, they feel, is in accord with the consistent physiologic observation that distention is the sole adequate stimulus to visceral pain.

PATHOLOGY

Although the nature of this paper does not permit a detailed analysis of the clinical and experimental observations concerning the etiology of ulcer formation, it is felt that a brief discussion of these factors is important at this point. This is felt to be true because the nature of past and current therapy is significant only as it relates to these factors.

It is generally agreed that although much is known about the etiology of gastric and duodenal ulcers, the exact cause is still unknown. Peptic ulcer is a very common disease. It has been stated that 10% of all adult males have or have had an ulcer (6). It is apparently a disease of civilization. It is primarily a disease of males, but no acceptable reason has been found why this should be true.

There are numerous opinions as to the etiology of peptic ulcer, but when all of the theories are analyzed, each of them appears to have basic factors to which most of them subscribe. For practical purposes peptic ulcers do not occur in patients with achylia gastrica, and they do not occur beyond the duodenum where the reaction is alkaline; therefore, hydrochloric acid and the digestive ferment, pepsin, appear to be necessary for the formation of an ulcer. Another factor which most people agree must be present is an area of devitalization of

tissue which permits the process of autodigestion and ulcer formation (6). However, the causative factors which bring about or permit the necrosis have been the subject of much controversy and speculation.

Among the causative factors, suggested as playing an important role in the development of peptic ulcer, are disturbances of enzyme balance (such as pepsin), disturbances of hormonal influences (such as enterogastrone), hyperacidity (as has already been mentioned), hypermotility, fatigue, psychic trauma or stress, body type, dietary excesses or imbalance, excessive use of alcohol or tobacco, focal infection, gastric or duodenal endartery thrombosis or spasm, excess vagal activity and allergy. The relative importance of any one of these factors or combination of factors is still unknown. Although none of these possible etiologic factors has been entirely discarded, pepsin imbalance, body type, allergy and focal infections are receiving little prominence in current medical literature.

Relatively recent investigations of certain gastrointestinal hormones and enzymes have been stimulating although by no means conclusive. Among this group are included: enterogastrone, anthelone, urogastrone, lysozyme, gastrin, secretin, pancreozymin, duocrinin and enterocrinin. Enterogastrone has been defined (7) "as a cholone (inhibitor) derived from intestinal mucosa,

which inhibits the motor and secretory activity of the stomach." Its action on the secretory and motor activity of the stomach was first observed by Kosaka and Lim in a study of cholecystokinin prepared by Ivy, Kloster, Lueth and Drewyer (9). Grossman (10) has said recently that "our latest studies have not been quite so encouraging but we are still convinced that an antiulcer factor is present in these intestinal extracts." Gambill, Morlock, Butt, Wollaeger and Code (11) state that the preparation of interogastrone which they used "did not produce sufficient benefit over and above conventional treatment of duodenal ulcer to encourage its use clinically".

Sandweiss, Saltzstein, and Farbman (12) first reported the isolation of anthelone as a constituent of the urine of pregnant women and later as a constituent of the urine of both non pregnant women and of males but little, if any, was found to be present in patients with duodenal ulcer. According to Sandweiss (7) anthelone exerts its beneficial effects not by inhibition of gastric secretion but by "promoting fibroblastic proliferation, new formation of blood vessels and epithelization of the mucosa". Urogastrone, first reported by Gray, Wieczorowski and Ivy (13), is a second constituent of urine which unlike anthelone, acts as a secretory depressant. However, the exact nature and place in

therapy for these hormonal subjects, as well as the others listed, is as yet undertermined.

Cushing (2, p.446) was the first within recent years to stress the importance of nervous influences in the pathogenisis of ulcer. He drew attention to the relatively high incidence of acute gastric ulcers after intracranial operations. Others previously had remarked upon the association of tumors of the mid-brain and diencephalon with gastric or duodenal ulcers, and the older pathologists had mentioned the softening of the gastric wall (gastromalacia) and other gastric lesions in subjects dying of cerebral conditions. Cushing suggests that the influences arising in the parasympathetic center in the pypothalmus and conveyed along the vagus nerves, are responsible for changes in the gastric mucosa which lead to the development of ulcer. Best and Taylor (2, p.446) state that the investigations of a number of workers support this conception. "Beattie, for example, produced areas of hyperemia and small erosions in the gastric mucosa (lesser curvature) by stimulation of the hypothalamus in the region of the tuber cinereum. Keller and his associates have observed ulcerations of the stomach and proximal duodenum with small hemorrhages, following lesions of the hypothalamus. Hyperemia and erosions of the gastric mucosa have also been produced

by the injection of pilocarpine (a parasympathetic stimulation) into the third ventricle or by continued stimulation of the vagus nerve." Babkin (2 p.447) suggests the possibility that vagal impulses cause the liberation of histamine in the gastric mucosa. Through its vasodilation action and stiumlating effect upon the parietal cells, conditions favorable to ulcer production are provided, namely, high gastric acidity and through capillary stasis, defective blood supply to the mucous membrane.

TREATMENT

The nature and effectiveness of peptic ulcer therapy are, of course, limited by our present knowledge of the etiology. Since this is still a controversial subject, therapy is at present chiefly aimed toward offsetting known factors in the abnormal physiology. Grossman (10) has written that "the aims of ulcer therapy can be simply stated. They are; (a) to control symptoms (b) to eliminate the ulcer either by causing it to heal or by removing it, and (c) to prevent a recurrence of the previous ulcer or the development of a new one." The last aim, as pointed out by Ivy (14) is at present the most difficult. Treatment is divided into the major subdivisions of surgery and medicine.

Current surigical procedures are intended to combat either the production or concentration of acid and in decreasing hypermotility. In regard to this last function, Nicheles (15) states that " a number of clinicians and investigators are coming more and more to believe that the prime factor in peptic ulcer and its distress can be found in motor disturbances of the upper gastro-intestinal tract."

Vagotomy first came into wider use in 1943 when Dragstedt and Owens (16) perfected the supradiaphragmatic approach. However, it was soon felt by many surgions that vagotomy has limited indications and was not without serious sequelae. Watters, Neibling, Bradley, Small and Wilson (17) state: "The greatest field of usefulness for the operation (vagotomy) seems to be in the treatment of ulcers after partial gastrectomy and in certain cases of non-obstructed duodenal ulcers in which the cephalic phase of gastric secretion is marked and pain is intractable." Maingot (18) warns that vagotomy is being carried out too frequently at the present time and he lists the following as indications "(a) Nervous patients under the age of 45 with uncomplicated duodenal ulcer--in whom repeated courses of treatment in a hospital have failed to effect a cure.

(b) Cases of chronic duodenal ulcer which give a history of repeated bleedings--(c) Cases of gastrojejunal ulcer which have followed a well performed gastroduodenal resection." There is agreement among other current investigators (19--22) that vagotomy, or at least vagotomy alone, should not be performed for gastric ulcer. According to Priestley (19) this hesitancy is due to staisfactory results having been obtained following gastrectomy without vagotomy and from associated ill effects on the rest of the intestinal tract.

The conventional medical treatment of peptic ulcer has been summarized by Ivy (14) as follows: "(a) physical and emotional rest, sedatives as indicated, and reassurance; (b) the buffering of acid with frequent small feedings, a highly nutritious diet to promote healing and taking advantage of the inhibitory action of fat on the bastric secretions; (c) antacid medicaments for the control of acidity, avoiding alteration of body chemistry as much as possible; (d) antispasmodics, as indicated and as tolerated by the patient; (e) continuous drip or therapeutic aspiration as indicated in special cases; and (f) the removal of foci of infection."

In speaking of the antacids, Grossman (10) states that: "(a) they leave the stomach rapidly and (b) they

do not always get well mixed with the acid gastric contents. The latter point is particularly true of the less soluble antacids such as are not widely used." He goes on to add that their limitations can be "illustrated by the fact that is has been estimated that in order to achieve satisfactory introgastric neutralization it is necessary to take as much as 10 times the amount of antacid that would be required to neutralize the stomach's secretion in vitro. A much better approach to the problem would be to stop the acid from being secreted."

In speaking of the inhibitory agetns, Grossman (10) states that : "the only important drugs now available for inhibition of acid secretion are atropine and atropine-like drugs." which in doses sufficient to effect inhibition, also cause "the distressing side effects of xerostomia and cycloplegia." In a discussion of peptic ulcer and its treatment, Necheles (15) says that "it is realized more and more, that the effect of atropine on volume and acidity of secretion in the normal subject and in the ulcer patient is so small, that it is often doubtful."

As for the future of ulcer therapy, Beattie (23) stated in 1949: "There seems to be little doubt that the final solution to the ulcer problem lies along medical

lines. It should not be beyond the limits of future possibility for suitable drugs to be developed to control the vagotonia which is the underlying cause of the ulcer diathesis." Grossman (10) has declared that "What is being sought is essentially a cholinergic blocking agent with specificity for site of action."

PHARMACOLOGY OF THE TETRAETHYLAMMONIUM ION

Comparatively little information has been recorded in the literature concerning the action of the tetraethylammonium ion, a quaternary ammonium ion. It was noted by Burn and Dale (24) in 1915, that TA was capable of preventing stimulation of ganglion cells by other quaternary ammonium compounds. According to Hoobler and Moe (25) Trendelenburg reported in 1923 that a marked depression ("fast vollständiger Stillstand") of the excised frog heart can be produced with a 1 per cent concentration of TA. This action of TA was not prevented by atropine, a fact which conforms with its generally accepted lack of muscarinic properties. Hunt (26) in 1926 confirmed the so-called "paralyzing nicotinic action" of TA.

TA has some similarities to veratrum alkaloids in its action on nerves. Cowan and Walter (27)

demonstrated in 1937 that TA causes isolated crab nerves to respond repititively to stimulation with single, brief shocks, and that it decreases the threshold voltage for slowly rising currents. Both of these properties are shared by veratrine as tested on circulated mammalian nerve (28). Intra-arterial injections of 10 mg/Kgm as tetraethylammonium bromide into the leg circulation of the cat produce the repetitive response to single brief stimuli the augmentation of negative after potential, and other related phenomena in the circulated peroncal nerve which veratrine also produces.

By far, the bulk of experimental work on TA has been done by Acheson of Harward and Moe and his associates of the University of Michigan Medical School. Acheson and Moe have studied the effects of the drug on the isolated dog heart (29) and on ganglionic transmission in dogs and cats (30) using as test responses the reactions of the blood pressure, heart rate and nictitating membrane. TA bromide injected intravenously in doses of 0.1 to 10.00 mgm/Kgm produced a prompt fall of arterial pressure in animals. They found that the depression response is not the result of a direct action of the drug on the arteriolar smooth muscle since while intravenous doses cause an increase in the volume of blood flow through

the femoral artery, intra-arterial injections of comparable doses cause no change. The blood pressure response is not due to a central action, but does not occur in the absence of vasoconstrictor tone. The drug causes no further fall of pressure after destruction of the medulla or section of the cervical cord. However, if vascular tone and blood pressure are restored by stimulation of the cervical cord distal to the point of transection, TA again causes a depressor response. If blood pressure is maintained by continuous infusion of epinephrine or angiotonin. TA causes no fall in pressure. "Thus the drug does not prevent the direct effect of epinephrine and the site of action must therefore be assumed to be in the sympathetic ganglia."

To prove that this action is in the ganglia, the effects of the drug on the transmission in the stellate ganglia were studied (30). Heart rate responses to ganglionic block would be expected to depend upon the existing balance between vagal and sympathetic tone. The drug produced no change in the rate of the denervated heart. They found that when vagal tone is relatively high as in animals under morphine--chloralose anesthesia, an increase of heart rate is the usual response to TA. Animals under barbital anesthesia, in which sympathetic

tone is high, respond with a decrease of heart rate. Section of the preganglionic stellate connections in such animals with a high sympathetic tone causes a decrease of heart rate. TA now will fail to cause a further change. If the heart rate is maintained at a high level by repetitive stimulation of the preganglionic fiber, the drug will again produce c ardiac slowing. If, on the other hadn, heart rate is maintained by electrical stimulation of the postganglionic connections of the stellates, no change in heart rate ıollows injection of the drug. "The site of action is therefore localized in the ganglia."

The ganglionic site of action has also been demonstrated in the superior cervical ganglion of the cat (31). In these experiments Acheson and Pereira demonstrated that if a sustained contraction of the nictitating membrane of the cat is induced by preganglionic stimulation of the cervical sympathetic nerve, TA causes relaxation of the membrane. The contraction caused by post-ganglionic stimulation is not affected by the drug.

In discussing their findings (31) Acheson and Pereira state that "TA does not possess most of the pharmacological properties characteristic of the otner quaternary

ammonium compounds." "TA has, if any, only slight and inconsonstant nuscarinic effects and no atropine-like effects on the nictitating membrane. Although it is quite similar to curare in blocking the transmission of impulses through autonomic ganglia, it has little, if any, curarizing action in skeletal muscle."

"The one predominant effect of TA is the block of transmission across autonomic ganglia. According to the terminology already in use, this block would be designated a 'nicotinic paralyzing' effect. For not only the effects of acetylcholine, but also those of preganglionic nerve impulses are blocked at this organ which is most closely associated with 'micotinic' effects, that is, the aautonomic ganglion. Yet the action of TA has little resemblance to that of nicotine. It lacks completely the stimulating property and all the other properties of nicotine except the power to block ganglia. If pharmacological effects are to be named after pharmacological agents, it would seem that the blockage of ganglia should be named after the substance which in the purest manner exemplifies this effect. A more satisfactory alternative is, however, to describe the action of the pharmicological agent in terms of the site and nature of its action. TA, then, over a wide range of doses exerts a specific ganglionic blocking action."

EFFECTS OF THE TETRAETHYLAMMONIUM ION ON MAN

Holt, Lyons, Neligh, Moe, and Hodges (32) of the University of Michigan published the first significant reports concerning the roentgenologic observations of altered alimentary function following autonomic blockace with the tetraethylammonium ion. In studying the effect of TA on four patients with cardiospasm they found that none responded to TA (although two of the patients were relieved of the cardiospasm by amylnitrite inhalation) as far as visible alteration in the appearance of the normal esophagus. However, "changes produced in the stomach, on the hand, were quite definite." Intravenous injection of TA resulted in prompt diminution of gastric muscular tone and generalized dilation of the stomach. All signs of peristaltic activity except a few marginal fibrillations stopped abruptly and remained quiet during the period of activity of the drug. There was no appreciable escape of barium through the pyloris. With a few exceptions, they found that intramuscular injections of TA produced the same results except that the effects of the drug appeared more slowly and lasted over a longer period of time. "In either case, the over-all appearance of the stomach was strinkingly similar to that seen following vagotomy."

These same workers (32) also studied the effect of TA on the small intestine by flouroscopic and roentgenographic examintaion. Their subjects were eight well nourished subjects who had no symptons or signs referable to the gastro-intestinal tract (preliminary control examination had been done when deemed essential). They felt that an outstanding finding in every patient who received either intravenous or intramuscular injections of the drug was the "profound degree to which propulsive movements of the intestine were inhibited. Even in the duodenum and proximal jejunum, where peristalsis is most vigorous, motility appeared to stop completely. Flroroscopically, it appeared as if one were observing the intestinal tract of a cadaver outlined by opaque medium." Of significance is their following observation: "Atropine alone, through its paralyzing action on the parasympathetic nervous system, and adrenalin, which stimulates the sympathetics, were found to produce some inhibition of intestinal motility, but the degree of chance was not so pronounced as it was with tetraethylammonium. Further, regular movements of the mucosa persisted despite large doses of either atropine or adrenalin." (Note: the underlining is that of this author.)

Dodds, Ould, and Daily (33) made a fluoroscopic study of the stomachs and duodenums of 20 healthy men between the ages of 21 and 55. Vigor of the peristaltic activity of the stomach was recorded and a plain roentgenogram of the abdomen was made three hours after administration of a barium meal. These procedures were repeated on a subsequent visit when 0.5 gram of TAC in 10% solution was given slowly intravenously and the effects of gastric and intestinal movement and tone were noted. In all patients peristalsis of the stomach and small bowel totally disappeared, on the average within three niumtes following injection. They state: "This effect was very striking; the stomach appeared as a large atonic bag." Peristalsis was absent on the average for 45 minutes. Movement returned sooner in the small bowel than in the stomach and the three-hour roentgenogram showed no change from the control study. Gastric emptying was delayed, however. All patients exhibited practically complete emptying of the stomach at three hours in the control study; after administration of TAC, nearly half of the patients had gastric retention varying from 25 to 70 per cent at three hours.

In discussing their observations, the authors state: "The appearance of the stomach after administration

of tetraethylammonium chloride is strikingly similar to that after vagotomy. ---At all events, any safe pharmacological method of blocking the vagal effects on the stomach, at present only possible by surgery, deserves thorough evaluation." (Note: The underlining is that of this author).

CLINICAL APPLICATIONS

The earlies report of the clinical use of TA in treatment of peptic ulcer is that of Lyons, Moe, et al (34) of the University of Michigan Medical School in 1947. These workers administered TA in the form of 10% solutions of both bromide and chloride salts. In general, 0.2 gram to 0.5 gram injected intravenously and intramuscular doses not exceding 20 mgm/Kg body weight were administered. They report that the cessation of gastr-intestinal motility observed fluoroscopically with the barium meal was apparent clinically. "In patients with pain associated resulting from a peptic ulcer the administration of the drug is followed by immediate relief of the pain and by a decrease in peristaltic sounds. As the effects of the drug wear off pain returns and peristalsis may be even more rapid." They go on to explain that TAC

not only produces a cessation of gastro-intestinal motility but also has significantly decreased the acidity and the volume of gastric juice in an unstimulated stomach. However they found that it did not alter the effect of histamine on gastric secretion.

In 1948, Brown, Posey, and Gambill (1) published their findings of the action of TAC on gastric acidity and motility in patients with duodenal ulcer. In one set of experiments 10 patients were studied. Free, and total acid levels were measured; during fasting state; at fifteen minute intervals until acidity was normal following a test meal and intramuscular or intravenous injection of one-tenth normal sodium chloride solution; at fifteen minute intervals thereafter and for two hours following a second test meal and saline injection; on the following day at fifteen minute intervals after a test meal and injection of TAC. In three patients all tests were completed in one day . in two, TAC was given with the first meal and saline with the second. Chloride content of gastric juice was determined. They found that free and total acid and gastric juice chloride levels usually increased following the test meal and simultaneous administration of saline. In all cases except one, free and total acid and chloride

levels in gastric juice were consistently and markedly reduced following administration of TAC with the test meal. Reduction in free acid levels averaged 44% when TAC was administ ered intramuscularly and 62% when given intravenously. Lack of effect in one case was attributed to underdosage of TAC due to obesity.

This same report tells of the effect of TAC on gastric motility in 6 cases of duodenal ulcer and in one case of gastrojejunal ulcer following gastrojejunostomy. In each case, ulcer symptoms were severe enough to necessitate hospitalization. Multiple studies were done in each case following installation of a special mechanism for measuring and recording pressures within the stomach.

While saline injections had no effect on gastric motility as indicated by changes in intragastric pressure, and test meals induced great activity, TAC produced complete cessation of motility in all cases. The average period of amotility following intravenous injection of TAC (300-400 mg.) was 39 minutes; after intramuscular injection, it was 1½-3 hours. Bowel sounds disappeared during the period of TAC induced gastric inactivity. In two patients, ulcer pain disappeared shortly after TAC therapy, simultaneously with abolition of gastric motility and for the same length

of time as depression of gastric acidity.

These in vestigators state that two prime requisites for healing of peptic ulcer are reduction in gastric acidity and motility; therefore, by virtue of its ability to effect such reductions, TAC may be adjunctively helpful in relieving peptic ulcer pain and distress, especailly in patients with hyperacidity and night pain.

Binter and Rankin (5) of Wichita, Kansas have published the most extensive and recent (September 1950) report on the use of TAC in the relief of peptic ulcer pain. Seventy male patients were admitted to the medical service in whose cases the diagnosis of peptic ulcers was established by clinical and roentgenologic study. Of these, 30 proved to be "readily amenable to simple therapeutic procedures of rest, diet, antacids and mild sedation." Forty were considered to be less amenable to simple therapy by reason of severity of symptoms, recurrence and chronicity or refractoriness of the ulcer and/or the patient to "standard treatment". Of the latter group of 40, 27 cases presented pain as an outstanding symptom. These 27 cases form the basis of the report. Among these, one ulcer was gastric in location, 3 were at the pyloric ring, 22 were duodenal ulcers and one was at the gastro-

jejunal stoma; 4 of the duodenal ulcers and 1 pyloric were penetrating; 2 were complicated by subtotal pyloric obstruction, and 1 by hemorrhage.

In the 5 cases of penetrating ulcer, or with penetrating type pain, administration of TAC was begun immediately upon admission because the need to control pain and clarify diagnosis was felt to be paramount. TAC administration was initiated upon admission by physicians other than the workers mentioned in 4 other cases.

Therefore, of the 27 cases forming the basis of the report, 18 cases were first maintained on standard management as a control. At that particular hospital, this treatment consisted of bed rest, tincture of belladonna minims 10, 3 times daily, phenobarbital gr. $\frac{1}{2}$, 4 times daily, 6 ounces of half milk-half cream, plus $\frac{1}{2}$ ounce of aluminum hydroxide--magnesium trisilicate gel (Gelusil) on alternating hours from 7:00 AM to 10:00 PM. If the pain was not lessened, the antacid was changed to sippy by addition of very bland foods, such as junket, soft cooked eggs and purees. A predigested protein suplement was given with milk in all cases. Where nocturnal pain was prominent the stomach was emptied by tube at 10:00 PM and 1 ounce of

gel was introduced before the tube was withdrawn.

The administration of TAC was begun upon the 18 control cases at varying intervals after beginning the above treatment. The decision to administer TAC came when complete reduction of pain had reached a stationary level. When administration of TAC was begun the diet was liberalized and belladonna, phenobarbital and antacids were discontinued. In the first case TAC was administered intravenously; thereafter it was given exclusively by the intramuscular route. Dosage was standardized at 500 mg. Eighteen cases were administered this dosage 2 times daily, 6 cases one time daily. Three cases received a single dose. Duration of administration varied widely.

These clinicians report that "complete relief of pain of peptic ulcer within 5 to 10 minutes after intramuscular administration of TAC was the rule. Recurrent pain could be consistently relieved by repetition of the drug. The five cases of penetrating ulcer admitted with pain simulating perforation were outstandingexamples. (Penetration or deep scarring was shown in three of these cases later subjected to surgery)" In the 4 cases where administration of TAC was not initiated by the authors of the report, relief of pain

was also consistent. The 18 cases submitted to a control period of observation under standard therapy before the the administration of TAC was responded upon its introduction with equally rapid relief of pain. Frequency of administration of TAC in all cases was determined by individual tendency to return of pain. Eighteen cases were given the drug twoice daily at 12 hour intervas; six cases received this medication daily at 12 hour intervals; six cases received this medication daily or less often; 3 cases received a single dose. (Note; underlining is that of this author).

The following two brief case histories are given as an example of pain relief by TAC in comparison with progress on standard therapy.

"Case 1. A 30 year old restaurateur first developed symptoms of epigastric distress 3 years ago. After hospitalization and examination he was given a medical discharge from the armed forces with a diagnosis of peptic ulcer. In the two years following his discharge he continued to be bothered several times a month with episodes of burning, cramping epigastric pain, coming on two or three hours after meals and frequently at night. For two months prior to entering hospital the patient had limited his food intake to goat's milk and

raw eggs, with frequent use throughout the day of alkaline powders. In spite of this, symptoms became worse so that one week before admission pain became constantly present and was associated with nausea and vomiting. Examination upon admission showed a well-developed and well-nourished adult male in acute distress. There was marked abdominal tenderness and rigidity, especially i n the epigastrium. The patient was afebrile. A roentgenogram of the abdomen in the upright position showed no free air in the abdominal cavity. Epigastric pain occured in frequent paroxysms which would cause the patient to double up in an effort to seek relief. During these paroxysms the blood pressure would rise from a normal level to 190/100 mm. Hg.

The patient was given 500 mg. of TAC intravenously and within 30 seconds after beginning the injection he became completely free of symptoms. After the completion of the intravenous injection he was given 500 mg. of TAC intramuscularly. Symptoms recurred in 12 hours and thereafter tended to recur daily in the early morning hours. His comfort was then maintained on a single daily injection of 500 mg. of TAC given at 5:00 AM. This was maintained until subtotal gastric resection on the 16th. hospital day. The pathologic specimen showed

a penetrating ulcer of the duodenum immediately distal to the pylorus. The ulcer was sharply punched out and had a floor of necrotizing granulation tissue with fibrosis extending through the muscularis and serosa. There was considerable induration and formation of adhesions about the anterior wall of the duodenum, extending posteriorly to the pylorus."

"Case 23. A 49 year old laborer had a 16 year history of repeated attacks of epigastric pain, with nausea and vomiting. Frequency and severity of attacks had gradually increased. Roentgen-ray examination upon admission showed a deformed duodenal bulb, with 60% gastric retention of barium at 5 hours. He was treated with standard therapy for 3 days with no improvement in symptoms. Twice daily administration of TAC was begun in 500 mg. doses. Pain was relieved immediately. Nausea and vomiting disappeared as nightly aspirations fell from a level of 1,000 cc to 200 cc over a period of 12 days. Roentgen-ray examination at this time showed no five hour retention. Administration of TAC was then discontinued. He remained free of pain and nausea, but gastric aspirations at 10 PM rose to a quantity of 1,000 cc after 11 days. Twice daily administration of TAC was resumed. Within 4 days

evening gastric aspiration fell to 300 cc. A subtotal ulcer with a floor of necrotic granulation tissue was found. There was marked contracture and deformity of the bulb with adhesions to the pancreas."

TOXICOLOGY

A comprehensive review of the toxicology of TAC has purposely been postponed until this portion of the paper and not included under the review covering the pharmacology of the drug. This was done in order that there would be a contiguous transition from the study of how TAC acts on the stomach in animals and men to the clinical findings in relief of ulcer pain etc..

Park, Davis and Company sells TAC under the trade name of "Etamon Chloride".(35). It is available in 20 cc "Steri-Vials" containing 0.1 Gm of TAC per cubic centimenter, or 2 Gm per vial. Park Davis and Company (36) give the following instructions regarding the dosage: "Etamon may be given in doses of 100 to 500 mg. (1 to 5 cc) intravenously, but not to excede 7 mg. per kilogram of body weight; intramuscular injections of 10 to 12 cc may be given (5 to 6 cc in each buttock). Frequency of injection will depend on relief of symptoms and tolerance of the patient. Two injections daily

have been administered for prolonged periods, although there may be some local soreness with repeated intramuscular administration." Lyons, Moe et al agree with this recommended dosage (34 and 37). They add that 1 cc of 2 per cent plain procaine hydrochloride solution to the dose of TAC which has decreased the discomfort caused by intramuscular injection of the drug.

Dodds, Oulds, and Daily (33) prescribe 0.5 grams of TAC in 10 per cent solution given intravenously for men of "average build", and 0.3 gram for men of "slight build." Binter and Rankin (5) state: "In our first case TAC was administered intravenously; thereafter it was given exclusively by the intramuscular route. Dosage was standardized at 500 mg. Eighteen cases were administered this dosage 2 times daily, 6 cases one time daily. Three cases received a single dose. Duration of administration varied widely."

Excretion of Tetraethylammonium (34): TA appears to be almost quantitatively excreted in the urine. It can be recovered from urine by precipitation with Reinecke salt as in the determination of choline. About 50% of the intravenous dose can be recovered in 30 minutes, while in 3 hours 50% of the intramuscular dose appears in the urine in the normal subject. Nearly all

can be recovered in 24 hours. With oral administration only 6 to 15% can be found in the urine in 24 hours, suggestin that it is poorly absorbed from the gastro-intestinal tract.

No major toxic effects have been observed from TAC when administered in amounts within the recommended range (5, 33, 34, 37, 38). However, TAC does produce physiological side effects that are not insignificant and they should be well understood by the physician and anticipated by the patient. Since the bulk of the work on this drug has been done by Lyons, Moe et al of the University of Michigan Medical School, the following summary of their work (34) is given.

The Effects of Intravenous Injection: The intravenous injection produces a metallic taste in the mouth in 15 to 20 seconds. This is followed by a sensation of numbness and coldness of the hands and feet in about 25 to 35 seconds with subsequent paresthesia which quickly disappears. Shortly thereafter there is an imcomplete dilation of the pupil and a decrease in its reaction to light. There is some loss of accommodation. Ptosis of the upper eyelids occasionally develops. The patient feels "tired," "relaxed all over," "weak. Within 30 to 60 seconds there

is a fall of both systolic and diastolic arterial pressures in the majority of patients with high arterial pressures and in some patients with normal blood pressure. (Dodds, Ould, and Daily (33) report that they found the average fall in systolic blood pressure to be 38.9 mm. of mercury and in the diastolic, 18.9 mm. when giving o.5 gram of TAC in 10% solution.) At the same time there is usually an elevation of the heart rate to between 90 and 120 beats per minute. Sweating, if present, stops. The mouth becomes dry. The temperature of the toes and fingers usually increases to that ofthe thigh or to about 33°C. The blood flow through the hands and feet as measured by the plethysmograph is increased. The systolic and diastolic pressures remain depressed for several minutes, then gradually increase to the initial level. Postural hypotension which develops immediately after the injection of the drug persists after the return of the blood pressure to its previous level and may last along with dilatation of the pupils and increased skin temperature for 15 to 60 minutes after a single injection. Vascular reflexes such as the effects of cold are abolished or greatly diminished at the height of the effects of cold are abolished or greatly diminished at the height of the effects of the drug. At the same

time there is cessation of propulsive gastro-intestinal motility so that barium in the gastro-intestinal track may remain in the same position until the effects of the drug diminish. The bladder tone is diminished and the urge to void with bladder distention is lost. In spite of the fall in blood pressure there is a temporary increase in the cardiac output of about 20% as measured by the Starr type of ballistocardiograph in normal and in hypertensive subjects having essentially normal control ballistocardiographic waves. Normal subjects and patients with elevated venous pressures experience a significant decrease in venous pressure.

Effects of Intramuscular Administration: The intramuscular injection of 1-2 gm. will produce the same effects over a longer period of time. The arterial pressure may be depressed in hypertensive patients for 2 to 8 hours. The skin temperature remains elevated and postural hypotension may persist over a longer period. The bladder atony becomes sufficiently pronounced so that the bladder may rise above the pubis, and the patient still has no desire to void. The gastro-intestinal tract remains quiet for several hours. During these effects, however, the patient is comfortable though there usually is weakness and faintness in the

sitting position due to the postural hypotension.

Effect on Kidney Function: Though pronounced changes in the blood pressure may be experienced in patients with hypertension, there has been no evidence of impaired kidney function after the intramuscular injections. The urine volume is moderately reduced when there is a significant fall in arterial pressure. The renal blood flow has been measured in sixteen patients by the clearance of paraaminohippurate. In normal subjects and in hypertensive subjects in whom moderate decreases in blood pressure were produced, clearance of para-aminohippurate was not significantly changed. The glomerular filtration rate as measured by the clearance of sodium thiosulfate was diminished in proportion to the fall in blood pressure. In animals with neurogenic hypertension, induced by elimination of the fubber nerves, the decrease in blood pressure resulting from administration of the drug was not associated with any change in renal blood flow as measured by a flowmeter or by the clearance of para-aminohippurate. Vasodilation is, however, apparently insufficient to maintain the renal circulation during the sudden and profound reduction in blood pressure occasionally noticed after the intravenous administration

of the drug in patients with very severe hypertension. Under these circumstances there has been a pronounced decrease in the renal blood flow and also a decrease in the formation of urine.

The Ann Arbor group (38) stated that in a few cases, peripheral circulatory collapse was noted, but this was of only transient duration and was readily relieved by artificial respiration, injection of a few minims of Adrenalin Chloride Solution, 1:1,000, and placing the patient in a moderate Trendelenberg position. Reardon, et al (39) have found that intravenous injections of neostigmine antagonizes the effect of TAC on autonomic ganglia and speeds recovery from postural hypotension.

Lyons and his associates (37) give the following precautions:

1. TAC should be used with caution in patients with severe hypertenion, particularly in the presence of poor renal function or a high diastolic pressure. It is not advisable to give repeated injections to patients who have impaired renal excretion. It should not be used in cases with a recent coronary thrombosis.

2. It should also be used with caution in elderly and arteriosclerotic patients who will often experience

a severe decrease in blood pressure and a diminution in blood flow in their legs during the hypotension.

3. Patients must be kept in a recumbent position for one hour following administration of the drug in order to avoid postural hypotension.

4. When temporary loss of ocular accommodation occurs, patients should not drive a vehicle for several hours following administration of TAC."

BRIEF COMPARISON WITH BANTHINE

Although the nature of this paper does not permit a detailed evaluation of the relatively new drug, Banthine (trademark of G. D. Searle and Company), since this would be ample subject material for another thesis; it is felt that brief mention of its pharmacologic nature should be made. This is done since the value of such a new and still experimental agent as TAC cannot be considered solely on the basis of its own clinical effectiveness and toxicology, but must be viewed in light of other current therapeudic measures. (There has been nothing in the literature comparing TAC with Banthine as far as could be determined by this author.) The following material on Banthine has been obtained from a recent publication (40) of G. D. Searle and Company.

Chemically, Banthine is a quaternary amine which is readily soluble in ordinary solvents and in gastric and intestinal secretions. Its descriptive formula is B-diethylaminoethyl xanthine-9- carboxylate methobromide.

As has already been discussed, TAC partially blocks in man the transmission of both sympathetic and parasympathetic ganglia. Banthine similarly acts as a ganglion blocking agent on both the sympathetic and the parasympathetic autonomic systems. However, Banthine also exerts "a potent additive atropine-like action at the postganglionic nerve endings of the parasympathetic system". "As might be expected, therefore, the principle site of action of the drug is on the 'parasympathetic system where it exerts a dual action, while it exerts a single and lesser action on the sympathetic system'". For this reason, a transient postural hypotension does not occur with Banthine as with TAC; in fact, a slight rise in blood pressure is the rule. Banthine has the added advantage in that its solubility and good absorption enable it to be taken orally.

The effect of Banthine on gastric motility and secretion seems to be approximately the same as with TAC when given in non-toxic doses; there is a sustained

diminution of motility and secretion. Although it is reported that Banthine administered orally in 50 to 100 mg. doses relieves pain in 15 minutes and gives sustained relief for a period of 5 or 6 hours, one does not get the impression that as spontaneous and complete relief is obtained as with TAC. The same article (40) reports that of 75 patients with ulcer-like pain prior to the administration of Banthine, 66 experienced no pain after the institution ofBanthine therapy and the remaining nine reported only infrequent or mild pain.

As has already been mentioned, Banthine has the advantage that it is effective when given orally and it does not lower the blood pressure but tends to elevate it slightly. Otherwise, the toxic effects of Banthine seem to be quite similar to those of TAC. These side effects are the result of parasympathetic inhibition and include mydriasis, drying of salivary secretions, varying degrees of urinary retention and difficulty in defication, and a generalized curare-like action with "considerable overdosage".

SUMMARY AND CONCLUSIONS

In order to discuss comprehensively the pharmacologic action of TAC on gastric behavior and thus its value in the treatment of peptic ulcer, the first one-third of this paper dealt with the pertinent points conerning the innervation and physiology of the stomach, the etiology and pathology of ulcer formation and the rationale of past and current ulcer therapy. Although numerous and varied opinions were presented, it is felt that the following points are pertinent in summarizing this portion of the thesis:

(A) The vagus nerves are predominately motor and stimulate motility of and secretion within the stomach; the sympathetics are predominately inhibitory. Acetylcholine is liberated at the synapse between pre and post ganglionic fibers of both the sympathetic and parasympathetic systems; the vagi also liberate acetylcholine between postganglionic fibers and effector organs. Motility and secretion are also both stimulated and inhibited by several hormones of as yet undertermined significance. Afferent pain stimuli are not transmitted by vagal afferent fibers but are carried by fibers coursing with the splanchnic sympathetics.

(B) There is nt general agreement as to the exact mechanism whereby the pain is produced in peptic ulcer. Binter and Rankin (4) offer an explanation which, this author feels, reconciles divergent views. They believe that chemical irritation of an ulcer crater produces local reflex spasm. Resulting hypermotility produces distention proximal to the site of spasm; distention of the viscus is the immediate origin of pain.

(C) There are numerous theories as to the etiology of peptic ulcer. Of the several factors or processes which seem to be implicated, there are two which appear to be of major significance. They are hyperacidity and hypermotility.

(D) Surgical and medical treatment of peptic ulcer has left much to be desired. The more radical surgical approach to the problem (vagotomy and resection) is now generally considered to be indicated only after more conservative therapy has failed. It is not without danger and must alter the normal structure and function of the gut. Conventional medical treatment consists chiefly of: psychotherapy, antacids, and atropine and atropine-like drugs to inhibit hypersecretion and hypermotility. Psychotherapy is a long and expensive affair. The antacids often leave the stomach rapidly and are needed in

relatively large amounts for effective intragastric neutralization. The effectiveness of atropine and atropine-like drug in inhibiting acid secretion and hypermotility is doubtful. Grossman (10) concludes: "What is being sought is a cholinergic blocking agent with specificity for site of action."

The remainder (two-thirds) of this paper consists of a comprehensive review of the literature on the pharmacology of TAC and its clinical use in the treatment of peptic ulcer. The following points are felt to be most pertinent in summarizing this portion of the paper.

(A) Tetraethylammonium is a quaternary ammonium compound structurally similar to acetylcholine. It has some similarities to veratrum alkaloids in its action on nerve. Experiments have been sited which demonstrate that TA blocks transmission through the autonomic ganglia. Although it is similar to curare in this respect, TA has little, if any, curarizing action on skeletal muscle.

(B) Roentgenologic observations of alimentary function following autonomic blockade with TA have been given. The overall appearance of the stomach was

strikingly similar to that seen following vagotomy. There is a prompt diminution of gastric muscular tone and generalized dilation of the stomach. Motility is also completely stopped in the stomach and duodenum. The results were much more pronounced than when atropine was given.

(C) Investigators have found that TA not only produces a diminution in gastric motility but also consistently and markedly decreases the acidity and the volume of gastric juice in the unstimulated stomach.

(D) Marked relief of peptic ulcer pain after administration of TAC was reported by all using the drug clinically. Binter and RAnkin (5) used TAC on a series of patients whom they felt had obtained all the pain relief possible from standard management. They felt that the results were dramatic and report: "Complete relief of pain of peptic ulcer within 5 to 10 minutes after intramuscular administration of TAC was the rule. Recurrent pain could be consistently relieved by repetition of the drug."

(E) Recommended dosages of TAC ("Etamon Chloride" Parke, Davis and Company) are 200 to 500 mg. (10% solution) intravenously; intramuscular dosage recommended is 1,000 to 1,200 mg for the average man.

Frequency of administration is determined by relief of symptoms and tolerance of the patient. TA appears to be almost quantitatively excreted in the urine when given parenterally. Nearly all can be recovered in 24 hours, suggesting that it is poorly absorbed from the gastro-intestinal tract.

(F) No major toxic effects have been observed from TAC when administered in amounts within the recommended range. However, the drug does produce physiological side effects that are not insignificant and should be well understood by the physician and anticipated by both the physician and patient. The most pronounced side effects are: diminution in arterial blood pressure, elevation of the heart rate, a feeling of weakness, incomplete dilatation of the pupil and some loss of accommodation, dininished sweating, dryness of the mouth, and a feeling of numbness and coldness in the hands and feet. The warnings are given: TAC should not be given to patients with severe hypertension or to patients with impaired renal function; it should be used with caution in elderly and arteriosclerotic patients; patients must be kept in a recumbent position for one hour following administration of the drug in order to avoid postural hypotension.

(G) A brief comparison of TAC with the relatively new quaternary amine, Banthine (G. D. Searle and Co.) was included. Banthine, like TAC, is also a ganglionic blocking agent for both the sympathetic and parasympathetic autonomic systems. However, Banthine also exerts "apotent additive atropine-like action at the postganglionic nerve endings of the parasympathetic system." As a result, its effect is primarily parasympatholytic and adverse cardio-vascular phenomena associated with sympatholytic phenomena are not present and its side effects seem less pronounced than with TAC. Banthine has the added advantage of being effective when taken orally. Otherwise, its ability to inhibit gastric motility and secretion and afford relief from ulcer pain seem to be quite similar to that of TAC.

The author of this paper has come to the following conclusions:

Laboratory and clinical experiments with TAC have demonstrated that chemical agents which are capable of simulating the beneficial effects of vagotomy should provide a great step forward in the treatment of peptic ulcer. The results obtained from the use of TAC indicate that research is proceding in the right direction.

Prevention of gastric secretion and hypermotility through a blockade of the autonomic ganglia is certainly more effective than neutralization of the intragastric contents or the use of atropine. That hypersecretion and hypermotility are important factors in the etiology of peptic ulcer seems probable, that they are of prime importance in ulcer pain seems certain. The literature, thus far, indicates that such cholinergic blocking agents do offer real relief from ulcer pain that was not seen before.

However, there seems to be little doubt that TAC, in itself, is certainly not the final answer to this aspect of ulcer therapy. Although the drug has been reported to be non toxic in therapeudic dosage, the ever present unpleasant physiological side reactions, and the danger of even more serious circulatory collapse are serious handicaps. Although the beneficial results obtained from the drug might far outweigh its toxic manifestations, its general use is still not indicated if another drug can produce the same therapeudic results with fewer side reactions. Banthine may already be that other drug.

In reviewing the literature, the author of this paper has formed the opinion that Banthine is as effective

as TAC in reducing gastric hypersecretion and hypermotility. This is understandable on a pharmacological gasis as has already been discussed. However, the dramatic relief from pain afforded by TAC in non toxic doses seems to be greater than that offered by Banthine in non toxic dosage. If this be true, its explanation is not so apparent. Since no controlled studies have been made to compare the two drugs, the apparent difference may be only due to the enthusiasm of those reporting on the drugs. Such an investigation might be of great value, for if it can be demonstrated that TAC is more effective than Banthine only then it can be truly said that TAC holds an important position in the current treatment of peptic ulcer.

BIBLIOGRAPHY

1. Brown, H., Posey, E., and Gambil, E.: Studies of the Effect of Tetrethylammonium Chloride on Gastric Motor and Secretory Function in Patients with Duodenal Ulcer, Gastroenterology 10:837-847, 1948.

2. Best, C., and Taylor, N.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, The Williams and Wilkins Co., 1945, pp. 447, 489, 516, 587, 943.

3. Grenell, R.: Howell's Textbook on Physiology, ed. 15, Philadelphia, Saunders Co., 1946, p. 227-228.

4. Smith, R., Ruffin, J., and Baylin, G.: The Effects of Transthoracic Vagus Resection upon Patients with Peptic Ulcer, South. M. J. 40:1-10, 1947.

5. Binter, P., and Rankin, T.: The Relief of Peptic tic Ulcer Pain by Tetraethylammonium Chloride, Ann. Int. Med. 33:649, Sept. 1950.

6. Schenken, J., and Burns, E.: The Gastrointestinal Tract, in the textbook, Pathology, W. A. D. Anderson, St. Louis, The C. V. Mosby Co., 1948, p. 817.

7. Sandweiss, D.: Enterogastrone, Anthelone and Urogastrone: A Review of the Literature and a Suggestion for the Organization of a National Committee for the Study of "Peptic" Ulcer, Gastroenterology 5:404, Nov. 1945.

8. Kosaka, T., and Lim, R. K. S.: Demonstration of the Humoral Agent in Fat Inhibition of Gastric Secretion, Proc. Soc. Exper. Biol. & Med. 27:890 (June) 1930.

9. Ivy, A., Kloster, G., Lueth, H., and Drewyer, G.: On the Preparation of "Cholecystokinin," Am. J. Physiol. 91:336 (Dec.) 1929.

10. Grossman, M.: Physiologic Principles in the Treatment of Peptic Ulcer, Cincinnati J. Med. 30:336 (July) 1949.

11. Gambill, E., Morlock, C., Butt, H., Wollaeger, E., and Code, C.: A Study of the Effect of an Orally Administered Enterogastrone Preparation on the Clinical Course of Patients with Duodenal Ulcer, Gastroenterology 14:228 (Feb.) 1950.

12. Sandweiss, D., Saltzstein, H., and Farbman, A.: The Prevention or Healing of Experimental Peptic Ulcer in Mann-Williamson Dogs with the Anterior Pituitary-like Hormone (Antuitrin-S): A Preliminary Report, Am. J. Digest. Dis. 5:24 (March) 1938.

13. Gray, J., Wieczorowski, E., and Ivy, A.: Inhibition of Gastric Secretion by Extracts of Normal Male Urine, Science 89:489 (May 26) 1939.

14. Ivy, A.: The Problem of Peptic Ulcer, J. A. M. A. 132:1053 (Dec.) 1946.

15. Necheles, H.: The Phenomenon of Peptic Ulcer, Am. J. Digest. Dis. 16:237 (July) 1949.

16. Dragstedt, L., and Owens, F.: Supra-Diaphragmatic Section of the Vagus Nerves in Treatment of Duodenal Ulcer, Proc. Soc. Exper. Biol. & Med. 53:152 (June) 1943.

17. Walters, W., Neibling, H., Bradley, W., Small, J., and Wilson, J.: Gastric Neurectomy; Anatomic and Physiologic Studies with Favorable and Unfavorable Results in the Treatment of Peptic Ulcer, Arch. Surg. 55:151 (Aug.) 1947.

18. Maingot, R.: Section of Surgery: Discussion on Vagal Resection for Peptic Ulcer, Proc. Roy. Soc. Med. 41:645 (Sept) 1948.

19. Priestley, J.: Vagotomy (Editorial), Surg., Gynec. & Obst. 86:114 (Jan) 1948.

20. Orr, I.: Section of Surgery: Discussion of Vagal Resection for Peptic Ulcer, Proc. Roy. Soc. Med. 41:639 (Sept.) 1948.

21. Marshall, S., and Phillips, E.: Gastric Surgery: A Review of the Literature, Gastroenterology 12:748 (May) 1949.

22. Walters, W., Brownson, B., and Phillips, S.: The Problem of Vagotomy in the Treatment of Peptic Ulcer, Kentucky M. J. 47:254 (July) 1949.

23. Beattie, A.: The Physiological Basis of Vagotomy, Brit. M. J. 1:607 (April 9) 1949.

24. Burn, J., and Dale, H.: The Action of Certain Quaternary Ammonium Bases, J. Pharmacol. & Exper. Therap. 6:417 (March) 1915.

25. Hoobler, S., Moe, G., Rennick, B., Neligh, R., and Lyons, R.: The Effect of Autonomic Blockade with Tetraethylammonium on the Renal Circulation in Dogs and in Normal and Hypertensive Patients, Univ. Hosp. Bull, Ann Arbor, 13:9 (Feb.) 1947.

26. Hunt, R.: Some Effects of Quaternary Ammonium Compounds on the Autonomic Nervous System, J. Pharmacol. & Exper. Therap. 28:367 (Sept.) 1926.

27. Cowan, S., and Walter, W.: The Effects of Tetraethylammonium Iodide on the Electrical Response and the Accomodation of Nerve, J. Physiol. 91:101, 1937.

28. Rosenbleuth, A., and del Poza, E.: Accommodation in Mammalian Motor Nerves, Am. J. Physiol. 136:629, 1942.

29. Acheson, G., and Moe, G.: Some Effects of Tetrethylammonium on the Mammalian Heart, J. Pharmacol. & Exper. Therap. 84:189 (June) 1945.

30. Acheson, G., and Moe, G.: The Action of Tetraethylammonium Ion on the Mammalian Circulation, J. Pharmacol. & Exper. Therap. 87:220 (July) 1946.

31. Acheson, G., and Pereira, S.: The Blocking Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat, J. Pharmacol. & Exper. Therap. 87: 273 (July) 1946.

32. Holt, J., Lyons, R., Neligh, R., Moe, G., and Hodges, F.: X-ray Signs of Altered Alimentary Function Following Autonomic Blockade with Tetraethylammonium, Radiology 49:603-610, 1947.

33. Dodds, D., Ould, C., and Dailey, M.: The Effect of Tetraethylammonium Chloride on Gastric Motility in Man, Gastroenterology 10:1007-1009, 1948.

34. Lyons, R., Moe, G., Neligh, R., Hoobler, S., Campbell, K., Berry, R., and Rennick, B.: The Effects of Blockade of the Autonomic Ganglia in Man with Tetraethylammonium: Preliminary Observations on Its Clinical Application, Am. J. Med. Sci. 213:315, 1947.

35. Research Dept. of Parke, Davis & Company: Etamon Chloride, A New Ganglionic Blocking Agent, Detroit, Parke, Davis & Co., 1949.

36. Research Dept. of Parke, Davis & Company: Etamon Blockade, Therapeudic Notes, Detroit, Parke, Davis & Co., (Jan,) 1948.

37. Lyons, R., Moe, G., Campbell, K., Neligh, R., Hoobler, S., Berry, R., and Rennick, B.: The Effects of Blockade of the Autonomic Ganglia in Man, Univ. Hosp. Bull., Ann Arbor, 12:33 (April) 1946.

38. Berry, R., Campbell, K., Lyons, R., Moe, G., and Sutler, M.: The Use of Tetraethylammonium in Peripheral Vascular Disease and Causalgic Disorders, Surgery 20:525, 1946.

39. Reardon, M., Marzoni, F., and Hendrix, J.: The Effect of Neostigmine (Prostigmine) on the Actions of Tetraethylammonium (Etamon) in Dogs and Man, Fed. Proc. 6:364 (March) 1947.

40. Medical Dept. of G. D. Searle & Co.: Recent Advances in Therapy of Peptic Ulcer, Chicago, G. D. Searle & Co., Vol. 27, 1950.