THESIS

THE EFFECT OF STIMULATION OF THE VESTIBULAR APPARATUS ON GASTRIC MOTILITY IN THE DOG

By

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A controlled study is presented demonstrating motility changes in the fasting stomach of trained dogs during and after vestibular stimulation. Two methods of stimulation were used.

The first method--binaural application of a galvanic current over the cocainized mastoid areas--produces fundic hypotonus and inactivity. There follows, in most cases, the appearance, development, and persistence of abnormal continual contractions, characterized by a 20 second rhythm on a low tonal level.

The second method--linear and vertical acceleration--elicits immediate inhibition of hunger contractions and vomiting in addition to the effects noted above.

The subcutaneous injection of prostigmine evokes a hyperactivity of the fasting stomach. This hypermotility is different from that produced by either method of vestibular stimulation.

Atropine, in small subcutaneous doses, inhibits prostigmine-induced activity, but has no effect on that produced by vestibular stimulation.

ACKNOWLEDGEMENTS

I wish to express my appreciation and gratitude to Professor Boris P. Babkin for the original suggestion of the problem and for his generous advice and criticism throughout the course of the study. I also wish to thank Dr. S. Dworkin for his cooperation and continued interest and Dr. S. Komarov for many valuable suggestions.

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INTRODUCTION

Part I - General introduction and historical background.

The external manifestations, such as pallor, sweating, salivation, and vomiting, associated with the various forms of movement sickness, including sea-, air-, and carsickness, especially the first, have been known for a great number of years. In spite of this knowledge of the obvious outward symptoms, however, little factual information of the concomitant physiological changes was known until recently.

Many theories have been proposed as to the original site of excitation. Included among these were rhythmical tugging and consequent trauma of the intestines, disturbed ocular sensations, irregularity and disturbance of the various proprioceptive receptors, excitation of the carotid sinus and aortic arch blood pressure regulating mechanisms, and abnormal excitation of the vestibular apparatus.

Since vertigo, nausea, and vomiting are notable signs of various pathological conditions of the labyrinths (11, 28) as well as marked outward manifestations of the different types of movement sickness, and since orientation in space is known to be the primary function of these receptors, it was strongly suggested that the sicknesses were due primarily or entirely to abnormal labyrinthine stimulation.

Lehmann (26), among others, noted the fact that deaf and dumb persons with diseases of the middle ear do not become

seasick. He demonstrated experimentally that animals, whose VIII nerves have been destroyed, do not become seasick. As confirmation of this observation, Kreidl (23) could no longer produce seasickness by subjecting animals to the stimulation of abnormal movement after bilateral destruction of the VIII nerve or bilateral labyrinthectomy.

Abnormal labyrinthine stimulation, therefore, is thought by most clinicians and investigators today (3, 6, 16, 19, 24, 26, 29, 38) to be the cause of sea-, air-, and carsickness.

Since the stomach participates in the complex phenomena of nausea and vomiting, it is desirable to know to what extent vestibular stimulation affects gastric motility. In spite of general familiarity with the gross aspects of nausea and vomiting, however, the exact effects of such stimulation on gastric motility has never been placed under systematic examination in controlled experiments.

A few isolated studies of the immediate effects of labyrinthine stimulation on gastric motility do appear in the literature, but even these few bits of evidence present conflicting observations and conclusions.

Studying the stomachs of normal individuals fluoroscopically after a barium meal, Roccavilla (35) found that a violent gastric contraction, in which the pylorus tended to approximate the cardia spastically, was almost always caused by stimulation of the labyrinths. As an adequate stimulus, he used 4 milliamperes of galvanic current for 30 seconds or an irrigation of the ear with 500 ml. of water at 15 degrees

Centigrade. In spite of the contraction, the subjects did not usually experience any perceptual symptoms.

Podesta (33) confirmed and Lebensohn (25) reconfirmed these findings.

The latter, however, continued the investigation with a graphic study of the fasting human stomach during and immediately after caloric and galvanic - binaural application of 5-6 ma. over the mastoid area - stimulation of the labyrinths. Both methods resulted in an initial rise in gastric tone followed by a fall in tone to below its original level. It was further demonstrated that the initial rise was not due to the labyrinths themselves, but, rather, to the stimulation of the adjacent skin area. The fall in gastric tone was associated with vertigo and nausea. Moreover, if the stomach had been in a phase of motility, the stimulus caused a cessation of movement until some minutes after the sensation of vertigo had passed.

Although these phenomena of the initial rise in tone, the subsequent fall, and the cessation of gastric motility are well shown in Lebensohn's published radiological pictures and graphic representations, the spastic contractions mentioned above as occurring in man are nowhere demonstrated. Moreover, in Lebensohn's previous communication (24) these contractions are not mentioned anywhere in spite of the fact that exactly the same published figures are used as evidence.

Ventura-Gregorini (42), studying dogs under anaesthesia, found no fall in tone of the cardia after labyrinthine stimulation with a current of from 10-15 milliamperes over the

mastoid area. If his method of preparation be considered, however, it is not surprising that no fall in tone was recorded. The abdominal wall was cut open and the exposed stomach withdrawn from the abdominal cavity. An incision was then made into the cardiac end of the stomach and a catheter, 1 cm. in diameter, introduced and sutured into the incision. After the stomach posterior to the cannula had been tied off by a strong ligature, forming a sac of about 30 ml. capacity, physiological saline at body temperature was introduced into the sac under pressure. The stomach was then replaced within the abdominal cavity, the whole being connected through the catheter to a manometer for recording during and after stimulation. It is no wonder that no further fall in gastric tone could be found on stimulation of the labyrinths.

It is clear that there is not only a scarcity of information concerning this problem, but that the facts, as stated, are in conflict. A systematic study under controlled conditions was thought advisable and necessary, therefore, in order to determine the immediate and secondary, or prolonged, effects, if any, produced on gastric motility by stimulation of the vestibular apparatus.

Part II - The motor activity of the fasting stomach.

The stomach of man and dog, as well as other mammals, demonstrates two main types of peristaltic activity depending on whether or not food is present. Since the contractions of the empty , or fasting, stomach offer less technical difficulties in recording, since they are more easily controlled, and since

they appear in a definitely defined time sequence, presenting periods of activity separated by periods of relative inactivity, this form of gastric motility was utilized as a base line on which the altering delineations due to labyrinthine stimulation might be studied more understandably.

Boldyreff (4) was the first to demonstrate that the fasting stomach of dogs and man exhibit alternate periods of contraction and quiescence. At a later date, Cannon and Washburn (9), in experiments on man, proved that these periods of activity were accompanied by the hunger sensation and that each individual contraction was synchronous with a hunger pang. It is from this set of experimental evidence that the periodic motor phenomena of the fasting stomach derive the name hunger contractions. Carlson (10) substantiated the previously known facts and, by graphic and radiological methods on man and dog, carried the investigation into the mechanism of the hunger contractions, subjecting the phenomena to numerous inhibitory and augmentatory conditions.

The following discussion is based completely on Carlson's investigations, unless otherwise indicated.

The peristaltic activity (40) of the fasting stomach is cyclic. At definite intervals, there occur groups of strong contractions frequently imposed on an increased gastric tone. The individual contraction first appears at the cardiac end of the stomach and passes posteriorly toward the pylorus, becoming stronger as it continues its course. Groups of these individual contractions are the hunger contractions periods.

They appear at various lengths of time, depending on the youth and vigor of the subject. In the very young dog, the separation between periods of activity may be as short as 2-3 minutes. In the old adult, the period of relative quiescence may last from 70-280 minutes. Moreover, the periods of activity themselves are longer in the young, 4½-5½ hours, than they are in the old, ½-2 hours.

There are definite characteristic forms into which the contractions group themselves. Carlson describes three distinct forms of hunger contractions.

Type I consists of single contractions of approximately 30 seconds' duration. At the beginning of a period, they may be weak and separated by relatively long intervals, 3-5 minutes. During the course of the hunger period, the contractions become stronger and follow each other at a more rapid rate, so that, finally, the time separating the individual movements is 30 seconds or less. At the end of the period, the contractions may come to an abrupt halt or may diminish gradually. The duration of each group varies from ½-3 hours.

Type II, a stronger form, appears on an increased gastric tone. Here, individual contractions follow each other in rapid succession with no intervening pause. The duration of the individual contractions varies between 20 and 30 seconds. Type II contractions may vary to some extent in rate and amplitude, but otherwise be continuous for an observation period of from 2-6 hours.

Type III hunger contractions, observed only in the most vigorous individuals or after prolonged periods of starvation,

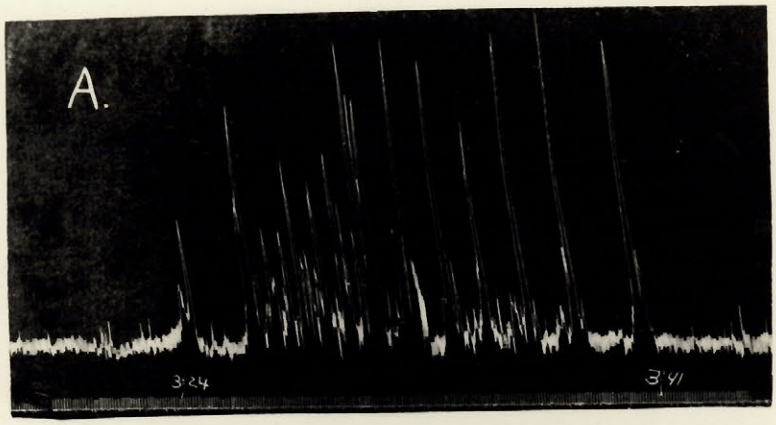
constitute an incomplete tetanus of the stomach on which are superimposed a series of rapidly recurring contractions. The contractions themselves may endure for from 12-16 seconds. This type usually marks the termination of a particularly strong hunger period, and ends abruptly. It may, however, constitute the entire hunger period, in which case, as with type II, it may continue for hours. On cessation of this type, there is a return to the resting tone of the period of relative quiescence.

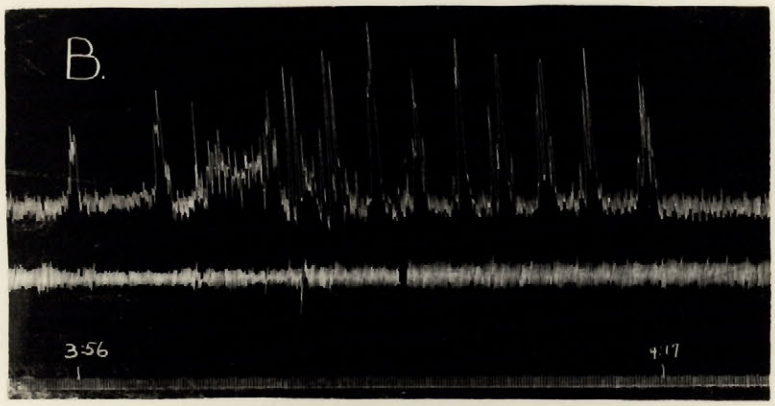
It is not to be thought that any one subject demonstrates exactly the same type of contraction from day to day. Although there is a definite consistency in the individual, the type of contraction may vary somewhat depending, primarily, on the general bodily vigor and the state of gastric tone at the particular time of the experiment. A normal subject, moreover, may demonstrate one or more types during a single period.

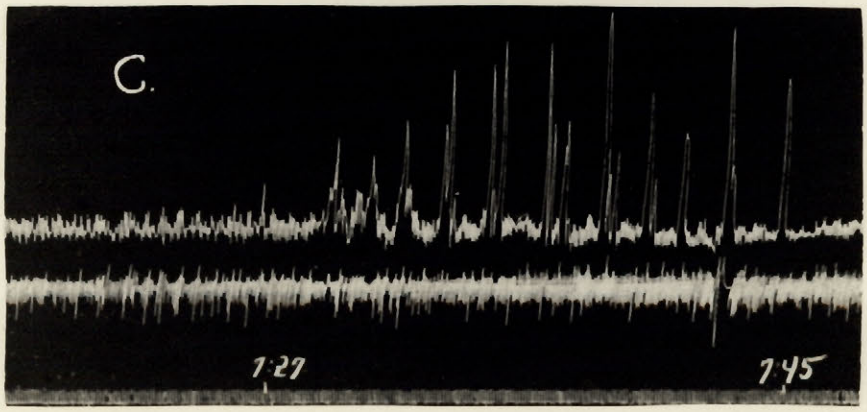
Fig. 1 shows normal hunger contractions from the three dogs used in the course of this study. Thus in A and B, the hunger contraction periods are characterized by type II at the beginning and type I at the end. C, on the other hand, is type I throughout. (The excursions traced between those of gastric motility and the time marking, 6 seconds /stroke, are those of respiration recorded by a pneumograph and a Marey Tambour.) The characteristic features of each type, as described above, are now visible.

Although Boldyreff and Cannon and Washburn believed that the stomach was completely inactive during the interval between

Fig. I







hunger contractions, Carlson proved that this was not so. Although the strong peristaltic movements do not generally occur--at times there may be small groups or single contractions appearing between the normal periods--there is a definite continuous, rhythmic movement consisting of slight changes in stomach tone. These appear as a 20 second rhythm of fluctuation in basic tone on which are superimposed the excursions due to respiration. Because of this tonus rhythm, or 20 second rhythm, the period intervening between those of normal hunger contractions is spoken of as one of relative quiescence.

Referring again to Fig. I, the tonus rhythm is evident in B at the end of the hunger period and in C before the beginning of the hunger period.

During prolonged starvation, hunger contractions are augmented, although the sensation of hunger decreases. This augmentation manifests itself in both the strength of the type of contractions, which usually procede to a type III during the later days of the fast, and in the duration of the contraction periods, which may eventually become continuous for three hours or more. Moreover, Luckhardt and Carlson (27) have shown that, if 30-50 ml. of fresh, defibrinated blood from a starving dog is injected into a normal dog while the latter is experiencing hunger, there is produced an immediate augmentation of the latter's hunger contractions.

In the same study as just referred to (29) Luckhardt and Carlson demonstrate an interesting effect on hunger contractions produced by acute hemorrhage. About one third of the blood

volume is withdrawn from the carotid artery, while the dog is under light ether anaesthesia. Within an hour and a half, during which time there has been a gradual return of the gastric tone, vigorous type III contractions begin and persist until the end of the observation period, up to 1½ hours. This augmentation disappears within 24 hours, so that a normal control exists on the day following the hemorrhage. As a probable explanation for this phenomenon, Carlson states, "The blood is, of course, the purveyor of nutritive substances to all the tissues of the body. Its chemical composition is kept remarkably constant. If now an animal is bled extensively, (2 to 3 per cent of body weight), there is removed suddenly an enormous amount of pabulum, that is, of those various substances which are taken up by different tissues during circulation. The organs and tissues deprived of these respective nutritive substances become hungry (call for food) by giving up a something (a hormone) which acts on the neuromuscular apparatus of the stomach to produce hunger contractions."

Augmentation of hunger contractions, as a delayed effect, is also produced by exposure to cold or strenuous physical activity, although the initial effect of these forms of stimulation is always in the direction of inhibition.

Hunger contractions may be inhibited by a number of different forms of stimuli, some of which are listed below.

1. Cerebral states, such as anxiety, fear, anger, eagerness, attention cause temporary inhibition. The inhibition takes place by way of

the splanchnic nerves, not by a depression of the vagus tone.

2. Stimuli from the mouth induced by the action of sugar, quinine, sodium chloride, weak acid solutions, etc. on the gustatory end organs; the chewing of indifferent substances; by chewing palatable substances. These too cause only a temporary inhibition which disappears after removing the substances from the mouth. In the case of palatable foods, however, the inhibition from the mouth may be replaced by inhibition due to psychic secretion into the stomach of acid gastric juice.
3. Stimuli from the stomach itself by the introduction of cold water, acids up to a concentration of 0.5 per cent, alkalies, in concentrations up to 1.0 per cent, and alchoholic beverages.
4. Inhibitory reflexes from the intestine are elicited by using normal gastric juice, pepsin in 0.2 per cent hydrochloric acid (0.1 - 0.5 per cent), neutral olive oil, fresh milk, etc.

Section of the vagus nerves in dogs leaves the stomach on the whole permanently hypotonic. The tone varies from day to day and occasionally may approach that of a dig with vagi intact, but usually remains low. Contractions themselves are changed mainly

in rate and regularity. The individual contractions appear normal or even slightly greater than normal, but are separated by intervals ranging from 2 to 8 minutes. They may continue for periods of time up to 3 hours or may be completely absent for like intervals. In this way, the periodicity of the gastric hunger contractions is obscured. On days, however, when gastric tone approaches that of normal dogs, the periodicity also tends to return to normal. Reflex inhibition of hunger contractions is still present, but seems to be less marked than when the vagi are intact.

Complete section of the splanchnic nerves in dogs, on the other hand, increases gastric tone and augments hunger contractions. In this case, also, the periodicity of the hunger contractions is obscured. They become more rapid and continuous, occurring about every 30 seconds for periods of from 2 to 4 hours, i.e. complete observation periods. In this case, however, when the gastric tone is low on any particular day, the contractions become less frequent and there is greater evidence of the periods of relative quiescence. After complete section of the splanchnic nerves, reflex inhibition of the hunger contractions is greatly diminished. The maximum effect of cerebral states is no longer complete cessation of hunger contractions, but, rather, a slight and transitory weakening of the contractions.

Section of both vagus and splanchnic nerves results in a condition similar to section of the vagus nerves alone.

The essential point is that, since the empty stomach, completely separated from the central nervous system , does exhibit typical hunger contractions, the primary role of the gastric nerves is that of modifying or regulating essentially automatic mechanisms in the stomach wall.

This necessarily broad and general outline depicting the normal and some abnormal forms of motility in the fasting stomach will serve as a background upon which the effects of stimulation of the semicircular canals may be more understandably oriented.

EXPERIMENTAL METHODS

Three normal, vigorous, healthy dogs were used as experimental subjects. The first, T, is young, weighing 32 pounds. The second, P, is an old adult, weighing 40 pounds. The third, J, is a middle-aged adult, weighing 48 pounds.

The animals were first trained to the physical conditions of the experiment, which require that they remain stationary and quiet for periods of time ranging up to seven hours. After having been placed in a standing position, they were comfortably supported from above. They soon adapted themselves to the supports and, away from all outside noises or excitement, learned to sleep during the greater part of the experimental time.

Within the course of this training, metallic gastric fistulae were inserted under aseptic conditions. Nembutal was used as an anaesthetic at these times which were the only occasions during which the animals were under general anaesthesia or any other artificial quieting influence.

As soon after the insertion of the fistula as was thought advisable, the dogs were placed on a standard balanced diet which remained unchanged during the course of the experimentation. The dogs were fed once a day.

The daily experimental procedure was as follows: About 18 hours <u>post cibum</u>, the subject was led from his usual surroundings to the experimental room. This schedule allowed ample time for the course of an individual experiment without

interfering with the normal feeding time. Although an occasional experiment might continue beyond the normal feeding time, an active secretion of gastric juice, psychic or otherwise, was never observed while the animal was in the experimental room. Having been placed on the stand and comfortably supported, the dog soon passed the period of excitement caused by the transfer from room to room. The metallic gastric fistula was then opened and the empty stomach gently swabbed to remove any mucoid material that may have collected there. A deflated balloon of thin rubber was then inserted through the fistula a predetermined distance into the stomach. The balloon was fixed in place by means of a cork, which had been pierced by large openings to allow any gastric secretion or swallowed saliva to flow out of the fistula rather than into the duodenum, or rather than to remain within the stomach and so act as a possible mechanical source of obstruction or stimulation. The still deflated balloon was then coupled to a bromoform manometer and air was injected into this closed system to a predetermined pressure, from 2 to 4 cms. of bromoform. In this way, a graphic record of gastric motility was obtained.

Stimulation of the vestibular apparatus was produced by two methods.

Binaural application of a galvanic current was the direct method. After the skin above and around the mastoid area had been cocainized by subcutaneous injections of a 0.5 mg per cent solution, small saline-wetted absorbent cotton leads were placed over the areas. A current of from 6 to 10 milliamperes for one minute or less

was then applied through these leads. The application of the stimulus was repeated up to seven times within the space of twenty minutes. This time interval between cocainization and the termination of stimulation was rigidly adhered to, so that no painful excitation could occur after the analgesia had worn off.

Although binaural stimulation of from 5 to 6 milliamperes was found sufficient to cause nystagmus in human subjects (25), this phenomenon was never observed in the dogs studied, although the strength of current was sometimes twice that previously used. This may well be due to the fact that, whereas, in the human the mastoid bone lies directly beneath the skin and permits a relatively close contact with the vestibular apparatus from the point of application on the skin surface, in the dog there is a large mass of muscle underlying the skin in this area, offering a much greater resistance to the passage of the stimulating current. In spite of the fact that no nystagmus was produced, there were definite movements of the head on making and breaking the circuit. On the make, the head turned toward the anode; on the break, the head turned toward the cathode.

It was not possible to obtain an adequate stimulus by irrigating the ear with cold or hot water. The fully conscious animal was most refractory to this form of stimulation. Indeed, much injury was done to one of the dogs by the shaking reflex induced by this stimulation and the subsequent irritation of gastric tissue by the relatively inert metallic fistula.

Linear and vertical acceleration were utilized as an indirect method of stimulation. This was accomplished by subjecting the animals to a swinging movement through an arc with a radius of 8 feet at a rate of 20 complete cycles per minute. The arc, varying in length from 5 to 8 feet, had a vertical component from the highest to the lowest point of from 4 to 8 inches. The duration of the swinging varied from 5 minutes, with susceptible subjects, to over 2 hours with a resistant subject.

The movements of the stomach were recorded before, during, and after such forms of stimulation.

EXPERIMENTAL RESULTS

About one hundred and seventy-five individual experiments, varying in time from 3 to 7 hours, were performed on the three animals.

Part I -- Control experiments.

At first, each subject was studied in a series of controls in order to determine the normal hunger contractions of that particular animal. Five to ten separate consistent recordings, each covering from two to four individual hunger contraction periods, were obtained from each dog before any deviation from normal conditions was attempted. In addition to this first series, controls were also interspersed among the series concerned with stimulation. As often as possible, every third experiment was devoted to a control study. In no case was there evidence of a prolonged effect within 24 hours after a period of stimulation.

Fig. I, already referred to, demonstrates the most persistent type of contraction period for each dog. They are as follows:-

Fig. I A - Dog J. Type II and type I. Duration of contraction period, 13 to 19 minutes. Usual, 17 minutes. Duration of period of relative quiescence, 110 to 130 minutes. Usual, 120 minutes.

B - Dog T. Type II and type I. Duration of contraction period, 15 to 26 minutes. Usual, 17 minutes. Duration of period of relative

quiescence, 70 to 90 minutes. Usual, 75 minutes.

C - Dog P. Type I. Duration of contraction period, 21 to 30 minutes. Usual, 24 minutes. Duration of period of relative quiescence, 90 to 105 minutes. Usual, 90 minutes.

Although there might occur minor variations in strength and duration of the hunger periods, this control record could be obtained at will.

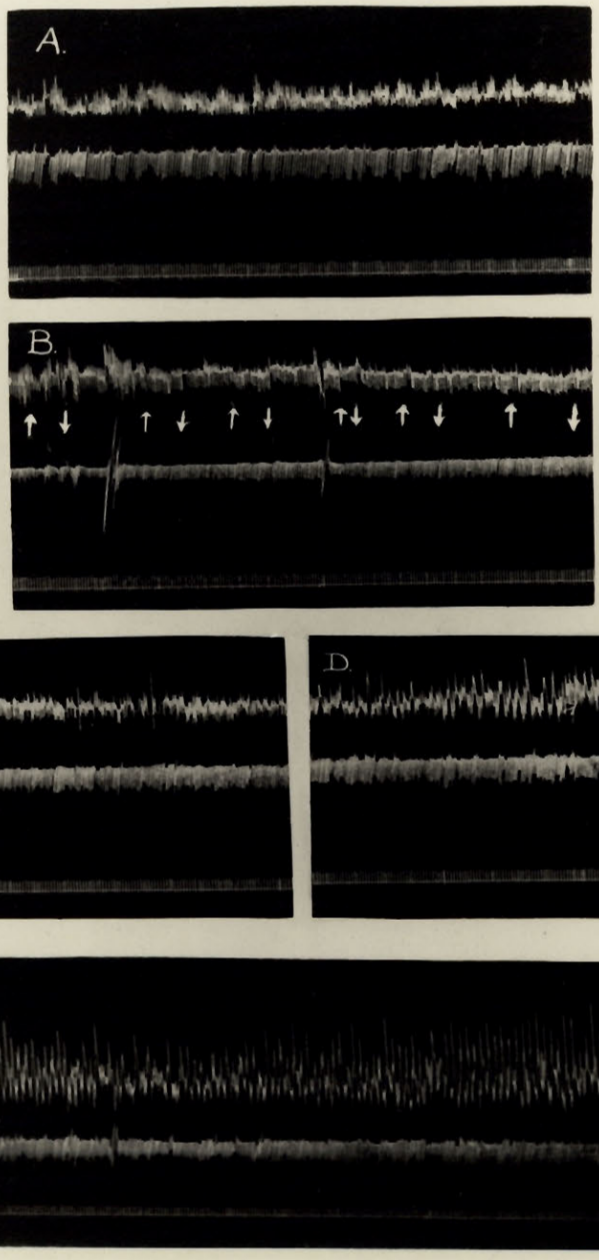
Part II -- Effects of binaural galvanic stimulation.

All the observed immediate and delayed effects of a galvanic current of 6 to 10 milliamperes over the cocainized mastoid areas are demonstrated in Fig. II, a record from dog T, experiment #51.

"A" represents the normal period between hunger contractions. Unfortunately, the delicate tonus rhythm is not so well recorded as in Fig. I B.

"B" includes the period of stimulation during which time 6 separate impulses were given. There is obviously no "spastic contraction" recorded, as was observed in man after a barium meal (25, 33, 35). On the first stimulation, however, there appears a transient rise in tone of 0.8 cm. of bromoform. On cessation of the stimulus, the tone returns to the resting level. Although this sudden rise does not appear during the two following periods of stimulation, there is a general increase of tone reaching 0.2 cm. of bromoform over the resting

Fig. II



level. During the last periods of stimulation, the tone falls to 0.6 cm. of bromoform below the resting level.

These immediate effects are followed by an inhibition of the appearance of normal hunger contractions. In dog T, whose quiescent period is normally no more than 90 minutes, inhibition has lasted as long as 192 minutes. During this prolonged interval the gastric tone remains low. In "C", immediately after stimulation, the gastric tone has dropped to 1.0 cm. of bromoform below the resting level. Careful observation shows that the tonus rhythm is already in evidence.

Even after this extended time of inactivity, however, normal hunger contractions do not usually appear. The 20 second rhythm, however, rather than continuing as such, undergoes a gradual augmentation until it has reached such proportions that it can easily be called a contraction.

In "D", ½ hour after stimulation and 106 minutes after the preceding hunger contraction period, the movements are already characteristic of a contraction. These contractions are fully developed in "E", 2 hours after stimulation, and continue so until the end of the observation period, ½ hour later.

Although these contractions answer Carlson's description of type III hunger contractions, they do not appear on a greatly increased gastric tone, but, rather, on a normal or, more generally, depressed tone. Because of this dissimilarity and the fact that its gradual development out of the tonus

rhythm may be repeatedly observed, this type of motor activity of the stomach will be referred to as tonal contractions.

Under the conditions of this form of stimulation, it was not possible to ascertain the immediate effects on hunger contractions themselves. The reaction to the subcutaneous injections of cocaine was sufficient in itself to inhibit continuation of a normal hunger contraction period, so that more than 20 minutes, the maximum period of time for stimulation after cocainization, passed before the continuation of the contractions would reappear. In view of the extensive period of training necessary to overcome this inhibition, and the fact that pertinent information was obtained utilizing linear and vertical acceleration, information which is in agreement with Lebensohn's published tracings showing the effects of galvanic stimulation in man, it is possible to suggest that the effect would probably be an inhibition of normal hunger contractions.

Control experiments, in which the mastoid areas were cocainized immediately after a hunger contraction period and the leads, placed as if for stimulation, were removed after 20 minutes, show a delay of from 20 to 30 minutes in the appearance of the subsequent hunger contractions, but, otherwise, no deviation from the normal.

Part III -- Effects of linear and vertical acceleration.

Because of the facility with which dogs are trained to accept this form of stimulation, the ease of application of the stimulus with adequate possiblity for variation in strength

and duration without causing injury to the dog, and the fact that the form of stimulation most closely approximates that existing normally, i.e. spatial change, this method primarily was used.

The immediate effect of swinging on the gastric motility of normal dogs is inhibitory to all normal movements, as regards both tone and hunger contractions, confirming Lebensohn's study with humans subjected to galvanic and caloric stimulation. This inhibition is evidenced in Fig. III.

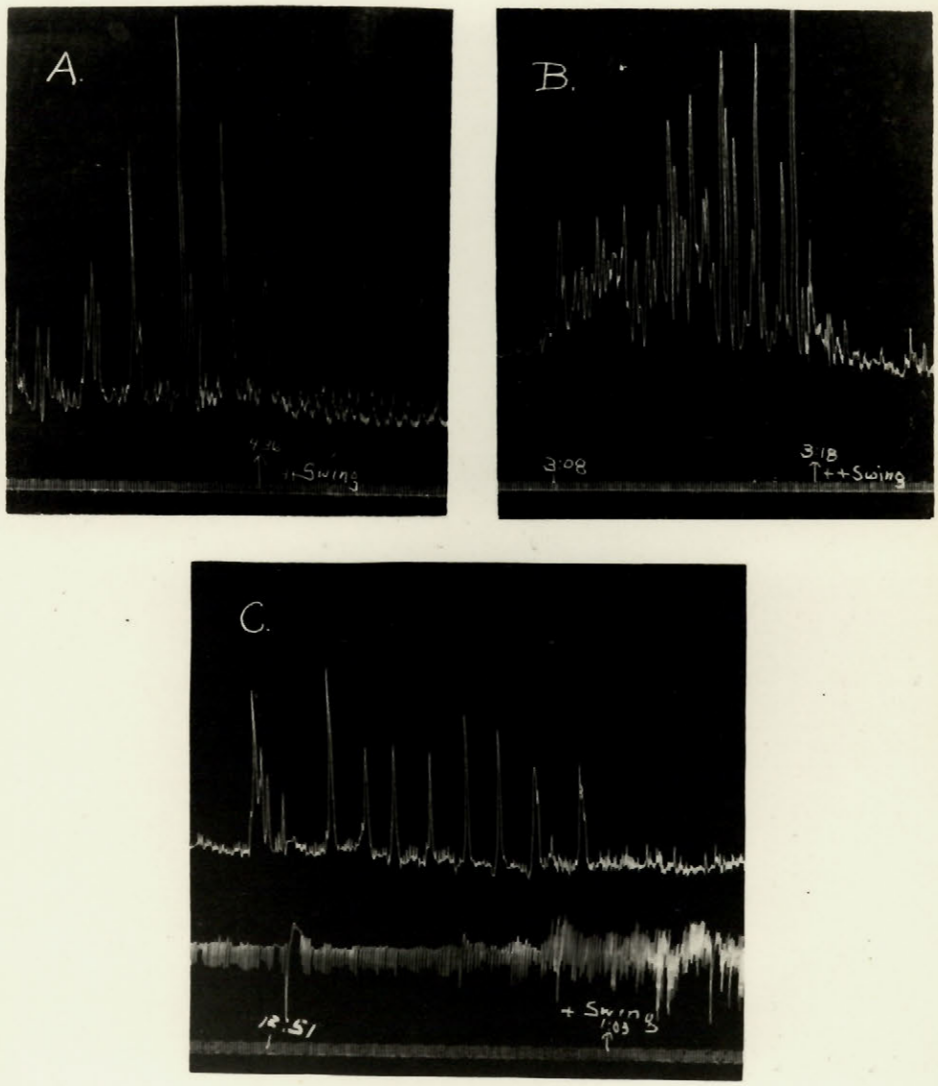
Fig. III A - Dog P, Exp. #52.
Immediate inhibition of type I hunger contractions. Fall in tone of 1.0 cm. of bromoform below resting level.

B - Dog J., Exp. #15.
Immediate inhibition of type II and I hunger contractions. Fall in tone of 1.0 cm. of bromoform below resting level and 4.0 cm. below point of highest tone during hunger contractions.

C - Dog T., Exp. #67.
Immediate inhibition of type I hunger contractions. Fall in tone of 0.6 cm. of bromoform below resting level.

Vomiting can be elicited from all three dogs studied if the stimulation is continued for a long enough period. There is, however, a considerable variation between individuals in susceptibility. Vomiting is easily produced in dogs T. and J.,

Fig. III



both reacting within 10 minutes from the commencement of swinging. P., on the other hand, is very resistant, requiring 1½ to 2½ hours of strong swinging before vomiting. If, however, after having been subjected to a prolonged period of stimulation without vomiting having been induced, he is returned to normal quiet conditions, a delayed hunger contraction appears within from 45 to 120 minutes afterward. During this hunger contraction period, he invariably vomits.

Dog T., moreover, showed a transition in susceptibility. On the first application, 25 minutes of moderate swinging were required to evoke vomiting. On each succeeding application, however, the time necessary to produce this reaction was reduced by 5 minute intervals until, finally, 7 to 10 minutes of moderate swinging became the persistent period.

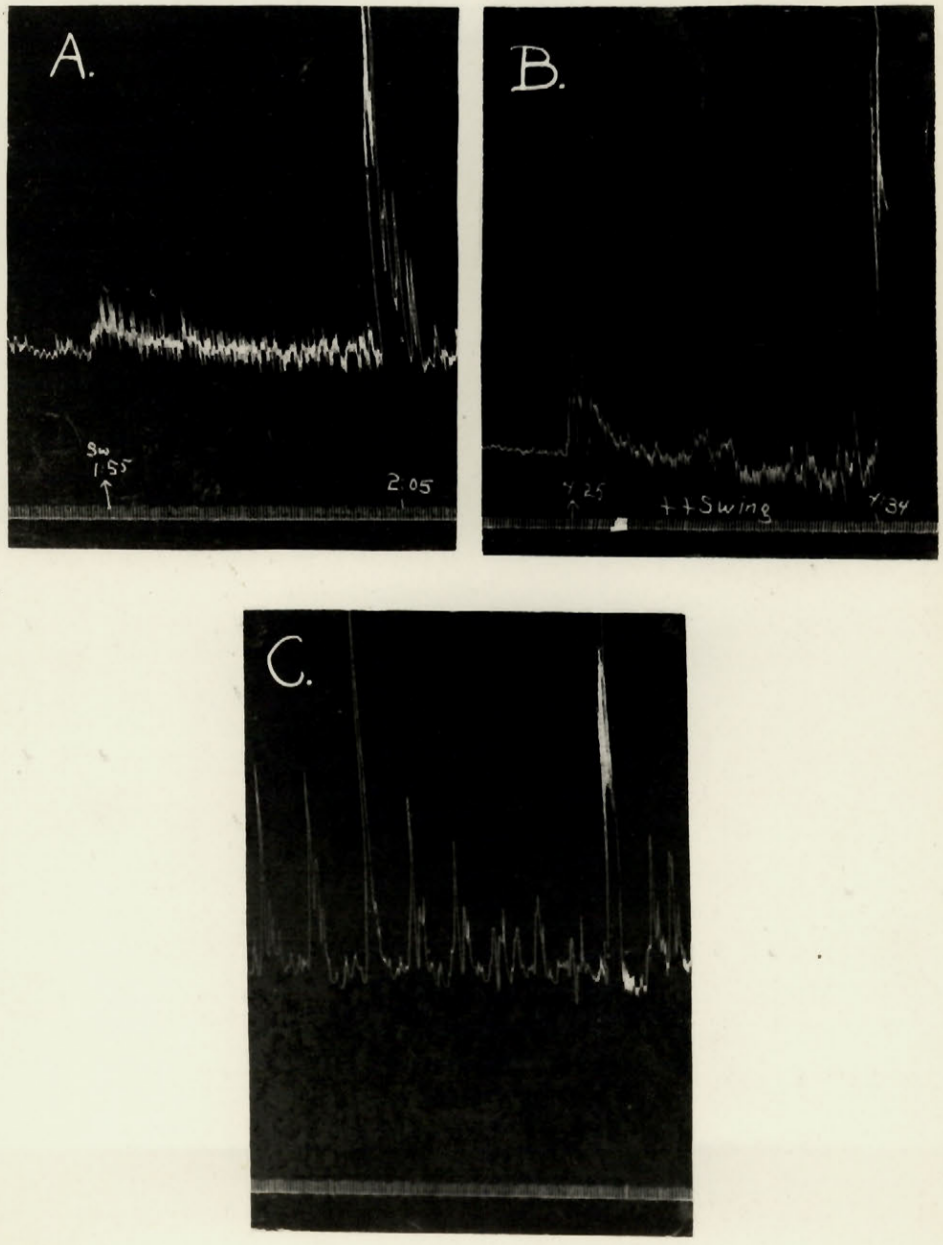
Fig. IV is a graphic representation of the act of vomiting in the dogs studied.

Fig. IV.

A - Dog T., Exp. #60.

Moderate swinging. Drop in tone of 0.6 cm. of bromoform below the resting level. (The apparent rise in tone at the beginning of the stimulation period is due to bracing and a consequent increase of abdominal tone.) During the fall in tone appear irregular waves of increased tone or contractions of small amplitude and extended duration up to 1 minute, which increased in amplitude

Fig. IV



and duration during the course of swinging. Vomited after 10 minutes of swinging, followed by a series of contractions on rapidly falling tone often present in this subject.

B - Dog J., Exp. #7.

Moderate swinging. Drop in tone of 1.6 cm. of bromoform below the resting level. Irregular contractions during later period of swinging. Vomited after 9 minutes.

C - Dog P., Exp. #49.

Has been subjected to strong swinging for 50 minutes. Hunger contractions start, 47 minutes after cessation of swinging and 103 minutes after previous hunger period. Vomited, 75 minutes after swinging stopped, during hunger contractions, which then continue unabated.

Stimulation of the vestibular apparatus induces three observed accessory phenomena which deserve mention at this time.

Yawning is the first noticeable symptom, an invariable external manifestation of stimulation, whether galvanic or linear and vertical acceleration. Within a minute after the initiation of stimulation, yawning appears, to continue throughout and for a variable period after the excitation.

Salivation closely follows yawning. Depending on the particular animal, the flow may be scanty, in which case there may be much chop-licking and swallowing so that no saliva appears from the mouth, or so copious as to constitute a continual drool. Salivation, also, continues for a variable time

after stimulation has ceased.

In the cases of dogs T. and J., vomiting is usually accompanied by the presence of bile in the stomach. Dog P. demonstrates this as an invariable concomitant of vomiting. The bile appears during the vomiting from both the fistula and the mouth, coloring the small amount of mucoid substance ejected during the retching movements.

This indirect evidence of increased intestinal activity confirms the observations of Spiegel and Demetriades (39) in acute experiments on dogs where an increase in tone and an augmentation of the pendular movements of the small intestines were produced by vestibular stimulation.

After the cessation of swinging, whether or not vomiting has been induced, hunger contractions may appear at the normal time, or, more often, after a prolongation of the quiescent period. This eventuality always occurs in dog P., occasionally in dog J., and rarely in dog T. The longest recorded inhibition of the appearance of the ensuing contraction period is 3 hours.

More often than normal hunger contractions, however, tonal contractions (cf. page 22) appear. This, also, is independent of the vomiting act. In dog P., who is highly resistant to vomiting, the tonal contractions appear during prolonged swinging. If the swinging is continued on a moderate scale, the contractions are preserved uninterrupted. If, however, the swinging is stopped at any time subsequent to their development, the tonal contractions are interrupted by the appearance of a normal hunger contraction period, to continue after these latter

movements have passed. The tonal contractions of dogs T. and J., however, once having started, usually continue uninterrupted until the end of the observation period, a time ranging up to 4 hours later.

In Fig. V, the appearance and development of tonal contractions are demonstrated.

Fig. V. Dog T., Exp. #60.

A - Immediately after swinging, as shown in Fig. IV A. Tone is 0,6 cm. of bromoform below resting level. Tonal contractions evident but weak, hardly greater than tonus rhythm.

B - 1 hour after swinging. Tone remains at same level. Tonal contractions strong.

C - 2 hours after swinging. Tone remains at same level. Tonal contractions fully developed. Continue until end of observation period, 1 hour later.

Fig. VI shows this phenomenon as recorded from the other subjects.

Fig. VI.

A - Dog J., Exp. #15.

Tonal contractions, 15 minutes after swinging short of vomiting. Continue until and through hunger contraction period, 95 minutes later.

B - Dog P., Exp. #52.

Tonal contractions during moderate swinging, which has been continuous for 2 hours. On cessation of swinging, contractions continue through following hunger contraction period.

Fig. V

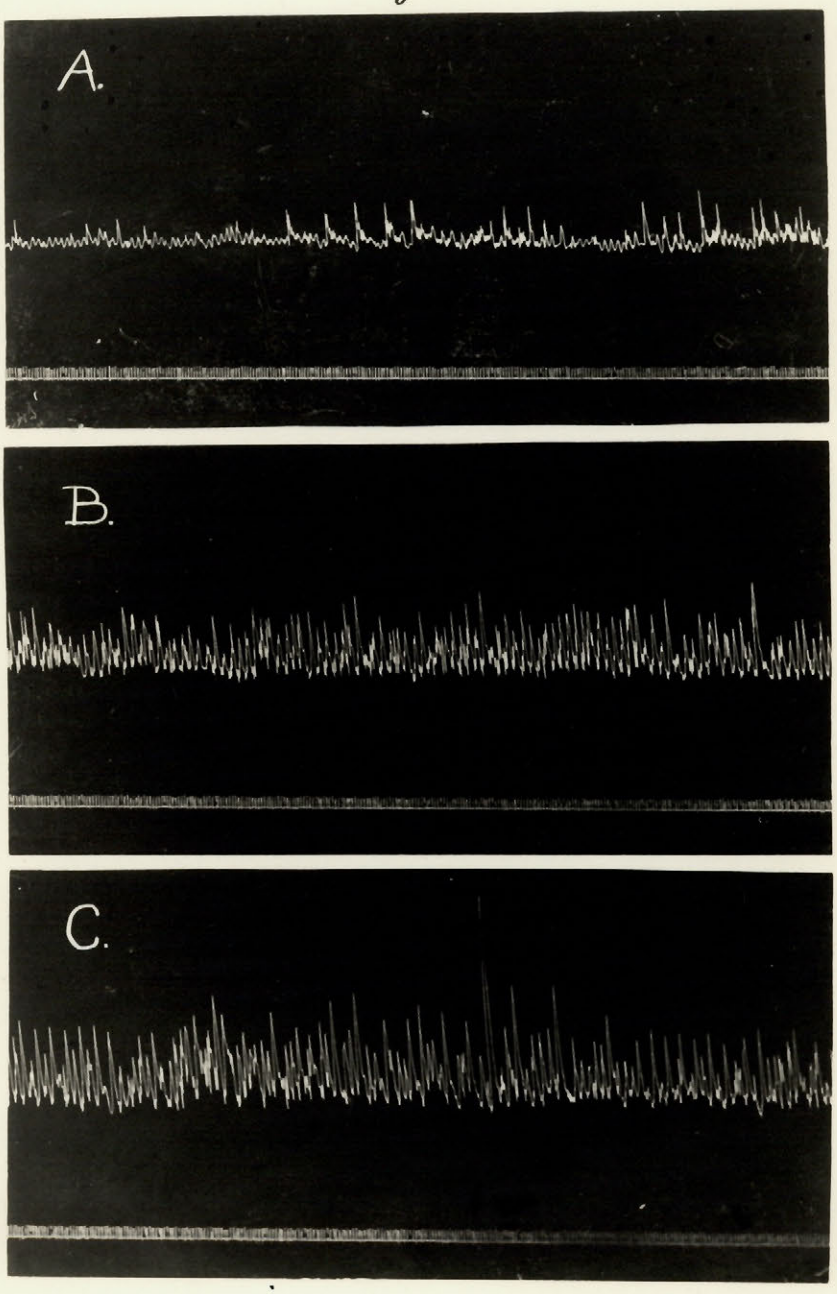
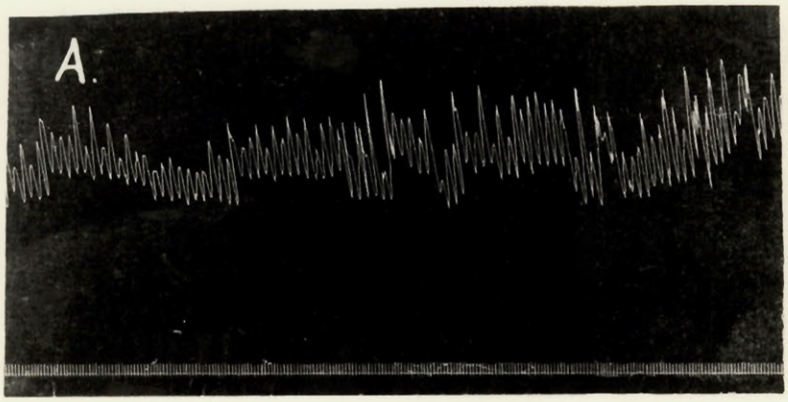
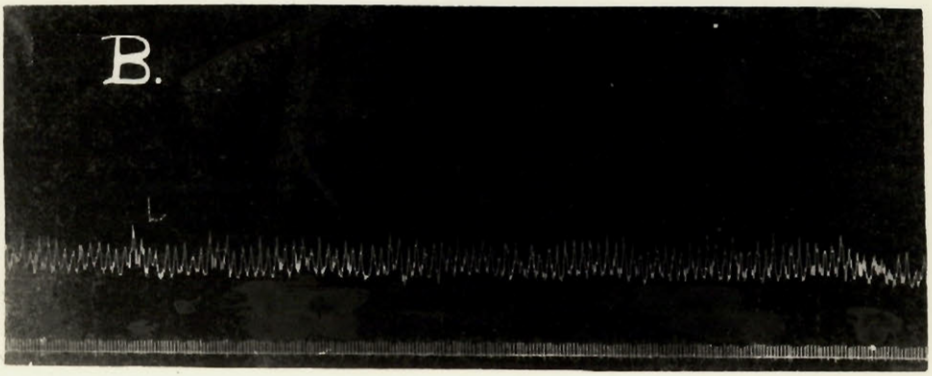


Fig. VI





In the above mentioned experiments, tonal contractions did not attain full development for periods of time ranging up to 2 hours after stimulation. During later series of experiments, however, when the animals, T. in particular, had been subjected to this form of stimulation 2 or 3 times a week for over 4 months, the tonal contractions occasionally occur fully developed immediately or within 25 minutes after vomiting or the cessation of swinging without vomiting.

During the course of these determinations, all controls were characterized by no deviation from the normal, although the dogs were placed and supported within the swing as if for stimulation. Moreover, swinging was never started until at least one normal hunger contraction period, in part or in whole, had been observed.

Part IV -- Effects of prostigmine.

Although there is no increase, but, rather, a decrease in gastric tone when the tonal contractions appear, they may be due to augmented cholinergic activity, particularly in the light of the similarity in form between these contractions and those of type III hunger contractions. In order to determine whether this augmentation was the cause of the prolonged subsequent effect, a group of experiments were conducted in which prostigmine, injected subcutaneously, was used as a means of increasing cholinergic influence on gastric motility. (Attempts were made to use acetyl choline itself, also by subcutaneous injection. Amounts up to 1¼ mg. per pound were injected without any noticeable effect on gastric motility.

This lack of observed effect may well have been due to the large amount of mucoid material which was secreted into the stomach under these conditions and the physical obstruction so produced, for the recording balloon was often found lying within the fistula on post-experimental examination.)

Most of the previous study of the action of prostigmine, or physostigmine, has been by roentgenological examination after a barium meal. Actually, the drug has been successfully used as an aid to such examination in patients whose gastric tone is very low, acting to increase the tone and to cause deep, powerful peristaltic waves (7). In the one study (41) of the action of prostigmine on the motility of the human fasting stomach, inhibition, manifested by a fall in tone and a cessation of contractions, was the observed effect in 78 per cent of the cases. Because of the side effects of salivation, slight diaphoresis, desire to urinate and defecate, and expulsion of gas <u>per rectum</u>, and the added fact that prostigmine, after a previous dose of atropine, produced a motor effect in 100 per cent of the cases, the observed inhibition may very well have been due to reflex activity from other organs affected by the dose of from 0.5 to 2.0 mg. of prostigmine by intravenous injection.

In the present study, a subcutaneous administration of ¼ mg. of prostigmine to a 30 pound dog--larger doses induce definite discomfort and, at times, salivation, urination, defecation, and vomiting (36)--decreases the duration of the period of relative quiescence and increases the duration, but

not the strength, of the hunger contraction period.

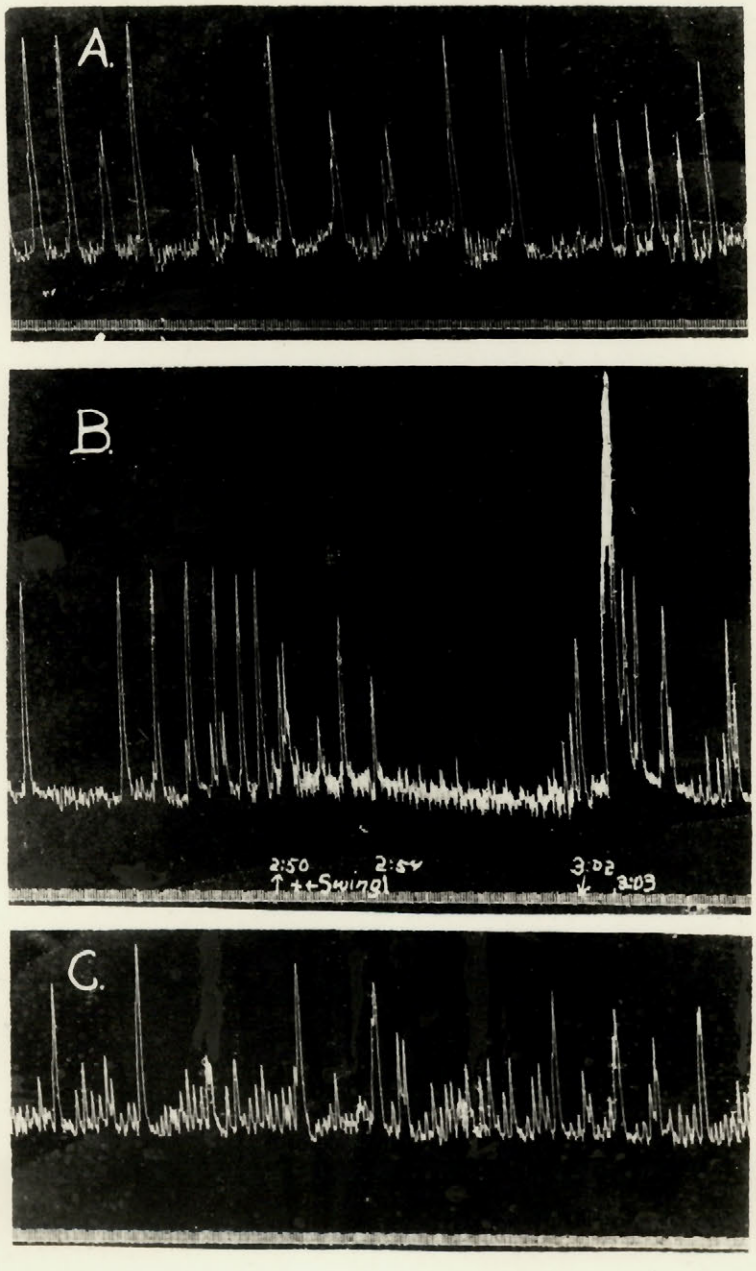
In order best to describe the action of prostigmine, the following facts are quoted as practically direct extracts from the protocols of a series of studies on dog T.

During the course of the first experiment, administration of the drug follows a hunger contraction period by 18 minutes. 28 minutes after the injection, a normal type I hunger contraction period starts and lasts for 16 minutes. The quiescent period, then, is 44 minutes, noticeably shorter than the normal. The second study demonstrates a lengthening of the hunger period to 25 minutes, still type I, with an intervening period of rest of only 23 minutes. This tendency increases until type I contractions start within from 7 to 10 minutes after the injection, although the injection may have been administered immediately following a normal hunger contraction period. Moreover, these contractions, once started, may continue practically without pause until the end of the observation period, sometimes as long as 4 hours.

This type I contraction, continuous after the administration of a $\frac{1}{4}$ mg. of prostigmine, is shown in Fig. VII A, a record from dog T., Exp. #80. This particular part of the record represents gastric motility 2 hours after administration of the drug.

It is evident that the prostigmine-induced contractions, under the maximum stimulation possible, in no way resemble tonal contractions induced by stimulation of the vestibular apparatus.

Fig. VII



Part V -- Combined effects of prostigmine and linear and vertical acceleration.

To press the above point farther, a series of studies were undertaken to determine the effect of combining the stimuli of prostigmine and linear and vertical acceleration by swinging. If the two different types of contraction were due to separate physiological agents, a combination of the distinct types of contractions might be expected from the excitation of their unique factors. That this is actually so is amply borne out in the subsequent observations.

In the earlier studies, prostigmine was first injected and time allowed for the full formation of the premature type I contractions. When these contractions had fully entered the picture, swinging was started.

The combined effect is shown in Fig. VII B and C.

Fig. VII.

B - Dog T., Exp. #83.

Swinging does not induce an immediate inhibition of the type I contractions, which continue for 4 minutes. The individual contractions, however, become weaker. In spite of the usual fall in gastric tone, 0.6 cm. of bromoform below the resting level, contractions reappear during the period of stimulation. Vomiting occurs within the usual time, followed by a continuation of the type I contractions. These type I contractions do not appear alone, however, as in

Fig. VII A, separated only by excursions due to respiration, but superimposed upon the tonal contractions, cf. Fig VIII A.

C - Dog T., Exp. #83.

1 hour after swinging. Type I contractions and tonal contractions both fully developed.

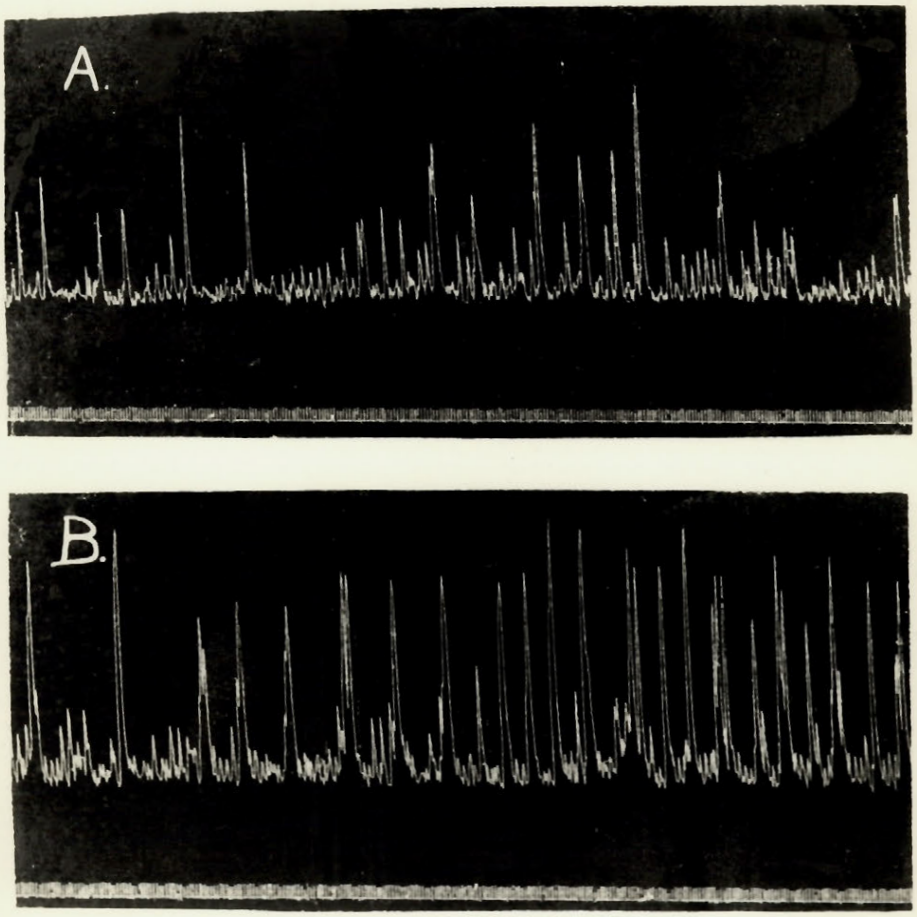
Although it is now obvious that the effects of prostigmine and stimulation of the vestibular apparatus on gastric motility are separate and distinct, there is evidence of interaction between the two. This is to be expected, since the two stimuli are acting on the same end organ and its neuro-muscular apparatus.

In Fig. VIII A, a record from the same experiment as described directly above, the tonal contractions are fairly well developed immediately after swinging. Since this experiment antedated by more than a month those in which the tonal contractions occasionally do occur well developed within ½ hour, it seems that prostigmine has an augmentatory effect on the tonal contractions at the beginning of their appearance. (cf. p.32)

As time procedes from the point of stimulation, however, the prostigmine-induced contractions attain their former vigor and gradually fall closer together. Finally, they become so strong and persistent as to drive the tonal contractions out of the picture, Fig. VIII B, two hours after stimulation.

As a last phenomenon, the type I contractions, which had begun 27 minutes after injection of prostigmine, stop, having continued uninterruptedly, except for the short period during swinging, for almost 3 hours. The stomach is quiet again.

Fig. VIII



The above experiments were conducted in a manner such that the effects of swinging were added to those of prostigmine. Precisely the same results are observed if the effects of prostigmine are induced after those of swinging. In this case, however, it is the appearance of the prostigmine effect which is hastened, coming in above the tonal contractions within 5 minutes after the injection. From this point, however, phenomena procede in exactly the same manner with the type I contractions contesting and finally overpowering the tonal contractions.

Part VI -- The effects of atropine on tonal and prostigmine-induced contractions.

Atropine, in subcutaneous doses up to 3.0 mg., has no effect on the tonal contractions.

If prostigmine has been injected after the tonal contractions have been elicited, the type I contractions appear, as described in the previous section. When the type I contractions have become fully developed, atropine, in doses of 1.0 mg., acts to inhibit and almost completely abolish the prostigmine-induced contractions and to preserve the tonal contractions which, otherwise, would have been obliterated.

DISCUSSION

In the present experiments, the motor activity of the fasting stomach of dogs has been studied before, during, and after stimulation of the vestibular apparatus. Two methods of stimulation were used. The first was produced by binaural application of a galvanic current of from 6 to 10 milliamperes over the cocainized mastoid areas. The second stimulus was swinging, which provided a combination of linear and vertical acceleration. That the results due to swinging are, in fact, elicited by vestibular stimulation is supported by the previous knowledge (23, 26) that movement sickness cannot be induced experimentally after bilateral section of the VIII nerve or bilateral labyrinthectomy.

In this discussion, the progressive development of effects, falling into three main categories--vomiting, inhibition of the subsequent appearance of hunger contractions, and tonal contractions-- will be dealt with in the order of their appearance. The first of these can be elicited by the use of linear and vertical acceleration; the last two are brought about either by direct galvanic stimulation or by swinging.

Some animals are more resistant to the experimental production of vomiting than others. This is shown by the difference existing between dogs T. and J., who react readily in from 7 to 10 minutes of moderate swinging, and dog P., who requires 1½ hours or more of strong swinging. This corresponds to the well known variation existing in human susceptibility to the different forms of movement sickness.

Although only vomiting and its associated movements, as demonstrated in this study, permit objective observation in the dog, it is safe to assume from numerous observations on man, as mentioned in the introduction, that the subjective sympton of nausea is also present both before, during, and for a variable time after the overt act. The facts presented, then, may be related to the phenomena known to occur in the fundus during nausea and vomiting.

Hatcher (17), in his review article, cites many observations of the inhibition of normal gastric peristaltic activity accompanied by atonicity of the fundus during the period preceding vomiting. Cannon (8), in radiological observations of the stomach of the apomorphinized cat, also described the inhibition of normal gastric motility. He further notes abnormal twitchings and contractions which start about 3 cm. below the cardia and move toward the pylorus. At the incisura angularis, however, he describes a deep constriction which divides the stomach. Actually, this may be the spastic contraction seen radiologically in man by Rocavilla, Podesta, and Lebensohn.

Disagreement exists as to the character of motility changes in the fundus during vomiting itself. Cannon describes a tightening of the gastric walls about the stomach contents during the repetitive spasmodic contractions of the abdominal muscles. Hesse (18), on the other hand, in a radiological study of dogs' stomachs, remarks that the fundus dilated and

remained flaccid. This observation was confirmed by v. Czhlarz and Selka (13) in humans.

In this study, the graphic representations of fundic activity, during linear and vertical acceleration and its consequent stimulation of the vestibular apparatus, confirm these previously described phenomena in the following ways:

1. Immediate inhibition of hunger contractions with a fall in tone of from 0.6 - 1.0 cm. of bromoform below the resting level. The fall in tone is evidenced whether the stomach has been in a phase of peristaltic activity or of relative quiescence. The fall in tone itself can be obtained by the use of either a galvanic or swinging stimulus.
2. A persistent hypotonus during swinging is interrupted by the appearance of abnormal twitchings, movements, or contractions which increase in amplitude as vomiting itself is approached. These abnormal movements are best shown by dogs T. and J.
3. Retching movements of the abdominal and diaphragmatic muscles are reflected within the stomach cavity and, consequently, are recorded.
4. Because of the effectual screening produced by the retching movements of skeletal muscle, it is not possible to determine by graphic methods whether or not the fundus exhibits any motility changes during the vomiting act itself. There are evidences, however,

of both a tightening of the gastric musculature and of a continued hypotonus. In the case of dog T., vomiting is usually followed immediately by a short series of abnormal contractions. These contractions start on a greatly increased tonal level which falls precipitously to a level below the normal resting level during the time of a minute or less following vomiting. Since the tone had been below the normal resting level immediately before vomiting, and since there is a greatly increased tone immediately after vomiting, it can be concluded that the increase in tone occurs during the vomiting act itself. On the other hand, dogs J. and P. demonstrate no such change. The tonus level is low both immediately before and immediately after vomiting.

In agreement with Lebensohn's observations in man (25), the tonal level remains low after stimulation and the return of normal gastric motor activity is delayed. In man, this delay was related to the feeling of nausea, persisting for some minutes after the sensation had passed. In the present study, hypotonicity and inactivity in the fasting stomach were produced as a secondary effect by both a galvanic and swinging stimulus and have been found to endure for periods of time ranging up to 3 hours after stimulation.

In about 80 per cent of the experiments dealing with vestibular stimulation, both by swinging and application of a

galvanic current, however, normal gastric hunger contractions do not appear at all. In their stead, the tonus, or 20 second, rhythm first becomes evident, increases in strength until it has attained an amplitude equal to the well developed peristaltic contraction of a hunger period, and continues for hours until the end of the observation period.

That these tonal contractions, as they have arbitrarily been named, are not identical with normal hunger contractions is concluded from a number of comparisons.

Normal hunger contractions are inhibited by swinging; tonal contractions are not inhibited by swinging and, in the case of dog P., even appear during the period of stimulation. In the case of this dog, also, tonal contractions continue after the cessation of swinging, but are interrupted by the appearance of a normal hunger contraction period, to continue after the normal form of movement has stopped. In the dogs studied, normal hunger contractions occur in periods lasting up to ½ hour; tonal contractions are not marked by any periodicity, but continue remarkably rhythmic and constant for as long as 4 hours. Although resembling type III hunger contractions in form, and these also may endure for greatly extended periods of time, tonal contractions appear on a tonal level below that of the normal, while the former are superimposed on a greatly increased tone which may constitute virtually an incomplete tetanus of the stomach.

If, then, tonal contractions are not part of the normal activity of the stomach, to what can they be attributed?

The effect might be produced either through nervous or chemical influences on the neuro-muscular apparatus of the stomach.

It is a well-known fact that, in general, adrenergic impulses are inhibitory to gastric motility and that cholinergic impulses are augmentatory, or motor, to gastric motility. Attempts were made, therefore, to increase cholinergic influences, and so duplicate the effects of vestibular stimulation, by injecting prostigmine subcutaneously to the limit of tolerance. The effects so produced proved completely negative as far as eliciting activity in the nature of tonal contractions is concerned. The activity elicited by prostigmine is not only different in form from tonal contractions, but can be produced in conjunction with tonal contractions, proceding to exclude them from their usual continuation. Further, prostigmine-induced contractions can be inhibited by atropine, which has no effect, in the dosage administered, on tonal contractions. These observations strongly suggest that the tonal contractions are not the result of increased cholinergic influence on or in the neuro-muscular apparatus of the stomach.

There is a possibility that they are due to some vascular changes and consequent blood-borne chemical agent acting directly on the stomach to produce the hypermotility.

The extreme pallor and greenish hue of the face and extremities, the lowered temperature of the extremities, and the fact that a prone position often serves to lighten the extreme subjective symptoms of seasickness have led many (6, 16, 19, 22, 31, 34) to the hypothesis that vascular

irregularities and, in particular, a pooling of blood in the splanchnic area, may be part of the syndrome of this illness.

Vascular changes have, in fact, been demonstrated after experimental stimulation of the vestibular apparatus. A number of investigators (14, 30, 32, 37, 38, 39) have noted a fall in arterial blood pressure. Actual alterations in blood volume distribution including rhythmical changes in peripheral volume (12, 32) and decreased splenic volume (5) have also been shown to occur as a result of vestibular stimulation.

Tonal contractions themselves are a definite, consistent, reproducible effect on gastric motility of both swinging and galvanic stimulation of the vestibular apparatus. The intermediate mechanism concerned in their production, however, is as yet unknown.

SUMMARY

A controlled study is presented demonstrating motility changes in the fasting stomach of trained dogs during and after vestibular stimulation. Two methods of stimulation were used.

The first method--binaural application of a galvanic current over the cocainized mastoid areas--produces fundic hypotonus and inactivity. There follows, in most cases, the appearance, development, and persistence of abnormal continual contractions, characterized by a 20 second rhythm on a low tonal level.

The second method--linear and vertical acceleration--elicits immediate inhibition of hunger contractions and vomiting in addition to the effects noted above.

The subcutaneous injection of prostigmine evokes a hyperactivity of the fasting stomach. This hypermotility is different from that produced by either method of vestibular stimulation.

Atropine, in small subcutaneous doses, inhibits prostigmine-induced activity, but has no effect on that produced by vestibular stimulation.

BIBLIOGRAPHY

(1) Alvarez, W. C. Reverse Peristalsis in the Bowel, a Precursor of Vomiting. J. A. M. A., 85, 1051, 1925.

(2) Alvarez, W. C. An Introduction to Gastro-Enterology. The Mechanics of the Digestive Tract. III Edition. Paul B. Hoeber, Inc. 1940.

(3) Blackham, R. J. Seasickness. Brit. Med. Jour., 2, 163, 1939.

(4) Boldyreff, W. (cited by Carlson) The Periodic Activity of the Fasting Stomach. Arch. Sc. Biol., VI, 1905, I.

(5) Bozzi, E. and Ciurlo, L. Volumetric Changes of the Spleen Following Labyrinthine Excitation. Arch. Ital. di Otol., 48, 83, 1936.

(6) Brooks, M. Seasickness. U. S. Navy Med. Bull., 37, 469, 1939.

(7) Butler, P. F. and Ritvo, M. Physostigmine, a Peristaltic Stimulant. J. A. M. A., 99, 1329, 1932.

(8) Cannon, W. B. The Movements of the Stomach Studied by Means of the Roentgen Rays. Am. Jour. Physiol., 1, 359, 1898.

(9) Cannon, W. B. and Washburn, A. L. An Explanation of Hunger. Am. Jour. Physiol., 29, 441, 1912.

(10) Carlson, A. J. The Control of Hunger in Health and Disease. University of Chicago Press, 1919.

(11) Cinelli, A. A. Clinical Forms of Labyrinthitis. Laryngoscope, 48, 157, 1938.

(12) de Crinis and Unterberger. Experimental Study of the Vascular Effects of Vestibular Stimulation. Zeitschr. f. Hals-, Nasen-, u. Ohrenh., 24,504, 1929.

(13) V. Czyhlarz, E. and Selka, A. (cited by Hatcher) Wien. Klin. Wchnschr., 26, 842, 1913.

(14) Demetriades, T. D. and Spiegel, E. A. Influence of the Labyrinth on the Function of the Carotid Sinus and Aortic Nerves. Ztschr. f. Biol., 98, 151, 1939.

(15) Desnoes, P. H. Seasickness. J. A. M. A., 86, 319, 1926.

(16) Forster, H. V. Seasickness and the Vestibular Nervous System - Theoretical Considerations. Proc. Roy. Soc. Med., 31, 96, 1937.

(17) Hatcher, R. A. The Mechanism of Vomiting, Physiol. Rev. 4, 479, 1924.

(18) Hesse, O. (cited by Hatcher) Pflugers Arch. clii, 1, 1913.

(19) Hill, J. Treatment of Seasickness. Practitioner, 38, 297, 1937.

(20) Ivy, A. C. and Vloedman, D. A. The Small Intestine in Hunger. Amer. Jour. Physiol., 72, 99, 1925.

(21) Keeton, R. W. Nausea and Related Sensations Elicited by Duodenal Stimulation. Arch. Int. Med., 35, 687, 1925.

(22) Keevil, J. J. Seasickness. Jour. Roy. Nav. M. Serv., 21, 216, 1935.

(23) Kreidl (cited by Fischer, M. H.) Handb. d. Norm. u. Path. Physiol., XV/1, 502, 1930.

(24) Lebensohn, J. E. Carsickness. Arch. Ophth., 4, 342, 1930.

(25) Lebensohn, J. E. Labyrinthine-Gastric Reflexes. Laryngoscope, 41, 175, 1931.

(27) Luckhardt, A. B. and Carlson, A. J. On the Chemical Control of the Gastric Hunger Mechanism. Am. Jour. Physiol., 36, 37, 1914.

(26) Lehmann, W. Vomiting. Klin. Wchnschr., 3, 1937, 1924.

(28) Mackenzie, G. W. Neurolabyrinthitis. Internat. Clin., 2, 126, 1938.

(29) Maitland, T. G. Cause of Seasickness. Proc. Roy. Soc. Med., 31, 96, 1937.

(30) Mies, H. Labyrinth and the Regulation of Blood Pressure. Ztschr. f. Biol., 97, 218, 1936.

(31) Nunn, P. W. G. Seasickness, Its Causes and Treatment. Lancet, 2, 1037, 1881.

(32) Pflanz, E. Etiology of Seasickness. Wien. Klin. Schnschr., 31, 896, 1903.

(33) Podesta, E. Reflex Excitability of the Labyrinth with Regard to its Relations to the Stomach. Ztschr. f. Laryng. u. Rhin., 17, 206, 1928.

(34) Poppen, J. R. Seasickness, Etiology and Treatment. U. S. Navy Med. Bull., 37, 463, 1939.

(35) Roccavilla, A. Gastro-Labyrinthine and Labyrinthine-Gastric Reflexes. Riforma Med., 38, 340, 1922.

(36) Schachter, M. Experimental Studies on Motion Sickness. Unpublished.

(37) Seiferth and Mark. Relation between Labyrinth and Circulatory Reactions. Ztschr. f. Hals-, Nasen-, u. Orenh., 34, 218, 1933.

(38) Sjorberg, A. Experimental Studies of the Eliciting Mechanism of Seasickness. Acta-otolaryng., 13, 343, 1929

(39) Spiegel, E. A. and Demetriades, T. D. Influence of the Vestibular Apparatus on Intestinal Motility. Monatschr. f. Ohrenh., 58, 63, 1924.

(40) Templeton, R. D. and Johnson, V. Further Observations on the Nature of Hunger Contractions in Man. Am. Jour. Physiol., 88, 193, 1929.

(41) Veach, V. O., Lauer, B. R., and James A. G. Effects of Prostigmine and Atropine on the Human Stomach. Jour. Pharmacol. and Exper. Therap., 62, 422, 1938.

(42) Ventura-Gregorini, F. Experimental Studies of the Effect of Labyrinthine Stimulation on Vomiting and the Tone of the Cardia. Arch. Ital. d. Otol., 51, 1, 1939.