THE MECHANISM OF THE VOMITING INDUCED BY ANTIMONY AND POTASSIUM TARTRATE (TARTAR EMETIC).

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The literature relating to the mechanism of the vomiting induced by tartar emetic does not afford a satisfactory explanation of the phenomenon, which has been a matter of dispute for more than two centuries. At present it is commonly accepted that this poison induces emesis reflexly through its action on the stomach or intestine, regardless of the method of administration. This view is based mainly on the results of experiments performed in Hermann's laboratory, and the prestige of Hermann's name caused the conclusions of his pupils to be accepted without a critical examination of the evidence which they submitted. Kleimann and Simonowitsch showed that traces of the poison—but only traces—were present in the vomitus following its intravenous injection. The fallacy of their conclusions lies in the fact that traces of tartar emetic are incapable of causing vomiting.

We wish to call attention especially to the observations of Harnack, who states that many dissimilar emetics, including tartar emetic, are capable of inducing paralysis of striped muscle of the frog, and who says that mention was made of this many years ago by Blake and by Orfila. Harnack also states that it may be accepted as a law that of those metallic salts which have no marked local action, only those which induce vomiting in mammals are capable of causing this depressant action on the muscles of the frog.

We have investigated the problem of the mechanism of the action of tartar emetic after having observed that the heart is the seat of reflex vomiting following the administration of the digitalis bodies, and we have endeavored to learn why different investigators came to such diverse conclusions. Limitations of space do not permit of a detailed

discussion of even the more important papers which deal with this subject, but we will give a partial list of them.

The present report deals with (1) the comparative emetic activity of tartar emetic by intravenous and oral administration; (2) the rôle of the vagus in emesis induced by tartar emetic; (3) experiments on the eviscerated animal; (4) the action of tartar emetic on the heart; and (5) the action of tartar emetic on the abdominal organs.

All experiments were performed on the cat unless the contrary is specifically stated.

1. Intravenous and Gastrointestinal Administration.

Magendie did not give the weights of the dogs or the concentration of the solutions used in his celebrated experiments, and while he did not state specifically that the stomach of the dog was filled with water before the tartar emetic was administered orally, one may infer from the context that it was, hence we could not repeat his experiments exactly.

In the present experiments tartar emetic was injected in 1 per cent solution intravenously into four cats in doses of 50, 35, 20, and 10 mg. per kilo of weight, respectively. The largest dose induced emesis in 7½ minutes; the next caused nausea in 10 minutes and emesis in 32 minutes; the third induced nausea in 13 minutes and emesis in 61 minutes; the smallest dose caused no perceptible effect in 6 hours, but the animal vomited during the night and was sick during the following day. All of the injections were made into the femoral vein within less than 1 minute, usually within 15 seconds. The protocol of one of these experiments follows.

Protocol Showing the Rapid Onset of Nausea and Vomiting after the Intravenous Injection of a Large Dose of Tartar Emetic.—Cat, female; weight 2.6 kilos. Animal fed meat about 5 hours before experiment. Mar. 20, 1922, 3.41^{20} p.m. 50 mg. of tartar emetic per kilo, in 100 parts of normal salt solution, into femoral vein. 3.42 p.m. Signs of nausea, licks lips, does not swallow. 3.42^{30} p.m. Signs of nausea positive, licks lips and swallows. 3.49 p.m. Vomited, after almost constant signs of nausea. 4.13 p.m. Defecated; killed.

We have compared the emetic activity of diluted and concentrated solutions of tartar emetic by oral administration to fasting cats and to those that had been fed only a few hours before the experiments. Similar doses were used in four experiments of this series.

50 mg. of tartar emetic per kilo of weight were administered through a stomach tube to each of two cats that had fasted for a period of about 24 hours. The first of these received a solution containing 1 per cent of the poison, the second received

a solution containing 0.1 per cent. The first vomited after 12½ minutes, the second after 83 minutes. This experiment was repeated with two cats that had been fed shortly before. The one that received the more concentrated solution vomited after an interval of 11 minutes, the one that received the more dilute solution after 27 minutes.

These results show that the concentration of the solution is of importance in determining the interval that follows before vomiting occurs after the oral administration of tartar emetic, and it is probable that whatever the concentration of the solution which Magendie employed it was greatly diluted by the water in the stomach.

Luckhardt, Phillips, and Carlson reported that vomiting is more easily induced by mechanical irritation of the duodenal, than by that of the gastric, mucosa, and it seemed probable that the duration of the interval following the oral administration of tartar emetic before emesis depends partly on the rate at which the poison passes through the pylorus. We therefore undertook to compare the activity of tartar emetic on the stomach with that on the duodenum and the jejunum.

A dose of 50 mg. per kilo dissolved in 100 parts of water was introduced into the stomach through a tube after the pylorus had been tied[1] in order to prevent the passage of any of the poison into the duodenum. This caused vomiting after an interval of 1 hour and 22 minutes. An interval of 2 hours and 29 minutes elapsed after tying the pylorus, before the tartar emetic was administered, hence there could be no question of interference with emesis due to the action of the anesthetic.

A dose of 20 mg. per kilo injected into the duodenum 7 cm. below the pylorus[1] caused slight nausea after 52 minutes, and vomiting 3 hours and 15 minutes after the injection. A dose of 5 mg. per kilo introduced into a loop of the jejunum[1] caused no perceptible effect within the period of observation—9 hours.

Vomiting frequently follows the operation of tying the duodenum and the injection of normal salt solution into a duodenal loop, hence we were unable to make a satisfactory comparison of the emetic action of tartar emetic on the stomach and that on the duodenum. Nevertheless, it seems certain that more of the poison is required per unit of area after its introduction into the duodenum than after its administration into the stomach.

[1] All operations were performed under chloroform anesthesia.

2. The Rôle of the Vagus.

The vagus is evidently concerned in the act of vomiting, but the rôle that it plays is not known with certainty.

Magnus says that Openchowski is the only one who has contributed to our knowledge of the nerve paths from the centers to the periphery whereby the contraction of the abdominal muscles, the gastric contractions, and the opening of the cardia are coordinated in the act of vomiting, and we know of no other contribution to this subject. Openchowski stated that the cerebral centers for contracting the cardia lie in the region of the quadrigeminate bodies, fibers from which run in the vagus mainly to end in Auerbach's plexus in the stomach; that the center for opening the cardia is at the point where the caudate nucleus unites with the lenticular nucleus, from which fibers run in the vagus to the lower part of the esophagus and the cardia; that there is also a center in the cord for opening the cardia. Openchowski classifies tartar emetic with those emetics which have a periphreal reflex action, and he states that the vagus alone is concerned in the emesis which they induce. Evidently he refers to the efferent path. It is well known, of course, that the vagus also carries sensory fibers for the stomach and intestine.

We sought to determine whether atropine is capable of preventing vomiting after the introduction of tartar emetic into different parts of the gastrointestinal tract and after its intravenous administration.

Each of six cats received an intramuscular injection of 1 mg. of atropine sulfaet per kilo of weight and after an interval of about an hour, designed to permit the full effects of the atropine to develop, tartar emetic was administered. Two of the animals received through a stomach tube doses of 50 mg. per kilo of weight, dissolved in 30 parts of water. One vomited after 56 minutes, the other had diarrhea after 65 minutes[2] and vomited 2 hours and 31 minutes after receiving the tartar emetic.

Four of the cats received intravenous doses of the tartar emetic, dissolved in 30 parts of normal salt solution. One received a dose of 80 mg. per kilo and died 10 minutes later without exhibiting signs of nausea; another received a dose of 55 mg. per kilo and showed no signs of nausea in a period of 62 minutes, after which it was killed; each of two other animals received doses of 35 mg. per kilo and showed nausea after intervals of 9 and 12 minutes, respectively, and both died without vomiting after a second dose of 30 mg. per kilo.

The intramuscular injection of 1 mg. of atropine sulfate per kilo of weight appears to delay the onset of vomiting following the oral administration of tartar emetic, and to prevent it altogether after the

[1] We have frequently observed that when diarrhea followed the intravenous injection of an emetic emesis was either delayed or absent.

intravenous injection of a fatal dose, and it seemed probable that an even larger dose of atropine might still further delay the vomiting following oral doses of tartar emetic or even prevent it altogether, though Sollmann states that a dose of 0.05 mg. per kilo causes paralysis of the vagi in the cat.

Each of two cats received an intravenous injection of 2 mg. of atropine sulfate per kilo of weight, dissolved in 500 parts of normal salt solution. After a few minutes a dose of 50 mg. of tartar emetic per kilo, dissolved in 20 parts of normal salt solution, was administered to each through a stomach tube. One cat showed slight nausea, the other showed no effect during a period of 5 hours, after which it was killed.

The results of these two experiments show that massive intravenous doses of atropine are more effective than even such large doses as we had previously employed by intramuscular injection for preventing vomiting after the oral administration of tartar emetic, but since nausea was induced in one of the animals, even such doses do not invariably paralyze all of the sensory endings, and it seemed probable that still larger doses of tartar emetic than those used might induce vomiting even after massive intravenous doses of atropine.

A ligature was tied just above the pylorus[1] in order to prevent any tartar emetic, which was to be given later, from entering the duodenum, the cat was allowed to recover from the effects of the operation and the anesthetic, after which a dose of 2 mg. of atropine sulfate per kilo was injected intravenously, and after about half an hour a massive dose of 100 mg. of tartar emetic per kilo was administered through a stomach tube. Nausea occurred after 2 minutes and emesis after 19 minutes.

Atropine usually prevents emesis following the introduction of normal salt solution into a loop of the duodenum, and vomiting occurred in only two of the seven control experiments in which observations were continued for periods of $1\frac{1}{2}$ hours, but it resulted promptly in every one of six experiments in which tartar emetic was introduced into a duodenal loop, following the administration of a very large dose of atropine.

A ligature was placed just above, and one just below, the pylorus[1] in each of two cats, after which each received an intravenous injection of 2 mg. of atropine sulfate per kilo of weight, in 500 parts of normal salt solution. After an interval

of a few minutes a solution of 35 mg. of tartar emetic per kilo, dissolved in 20 parts of water, was placed in the duodenal loop. One animal vomited after 15 minutes, the other after 20 minutes, showing that even this dose of atropine had no perceptible effect on the action of tartar emetic, except to delay somewhat the onset of emesis. Two nearly similar experiments were performed, but the duodenal loops were somewhat larger, and doses of 25 mg. of tartar emetic per kilo were used. Both animals vomited promptly.

TABLE I.

Effects Following the Introduction of Tartar Emetic or Normal Salt Solution into Loops of the Duodenum after the Administration of Atropine Sulfate.

Dose of tartar emetic per kilo.	Volume of solution.	Interval.	
		Before nausea.	Before emesis.
mg.	*cc.* × *kg.*	*min.*	*min.*
25	0.5	6	8
25	0.5	8	10
35	0.7	20	26
35	0.7	16	24
35	0.7		20
35	0.7		15
Control experiments with normal salt solution.			
	1.0		
	1.0		
	1.0		15
	0.7		
	0.7		22
	0.7		
	0.7		

Small loops were prepared[1] in two other cats, after which amounts of atropine corresponding to 0.2 and 0.3 mg. per kilo respectively were placed in these loops in order to secure the maximum of local action of the atropine, and after an interval of a few minutes a dose of tartar emetic similar to those used after the intravenous injection of atropine (35 mg. per kilo) was placed in each of the loops. One animal vomited after 24 minutes, the other after 26 minutes. The amounts of atropine which were placed in these loops were much smaller than the totals of those injected intravenously, but far larger than those which could come into contact with such small loops of duodenum after the intravenous injection of the larger doses. The tartar emetic must act locally in such cases because atropine prevents vomiting after the poison has been injected intravenously. The results of the experiments in which atropine was used and the duodenal loops were tied off are shown in Table I.

We also determined the effect of cutting the vagi on the emetic action of tartar emetic placed in the stomach, in the duodenum, and that following its intravenous injection.

A tracheal cannula was inserted[3] and the vagi were cut[1] in each of twelve cats. After an interval, sufficient to permit the animal to recover from the operation, tartar emetic or normal salt solution was administered.

Doses of 50, 75, 100, and 100 mg. of tartar emetic per kilo, respectively, were administered through a stomach tube to four of the cats; all showed nausea during periods up to an hour, and one of those which received the largest dose vomited after an interval of 2 hours and 38 minutes. One of the cats which had received a dose of 100 mg. was given a similar dose after an interval of 2 hours and 38 minutes. It died 3 hours and 15 minutes after the last dose without vomiting.

Each of two of the vagotomized cats received a dose of 35 mg. per kilo in a duodenal loop[1] similar to those previously described; one vomited after 15 minutes —exactly the same interval as that which followed the use of a similar dose in such a loop with the vagi intact in a cat which had previously received an intravenous injection of 2 mg. of atropine sulfate per kilo. The second cat exhibited nausea after a few minutes, with great respiratory disturbance, and emesis occurred only after 2 hours and 42 minutes. The introduction of a dose of 25 mg. per kilo caused nausea but it failed to induce emesis in one experiment. Two control experiments were performed in each of which 1 cc. of normal salt solution per kilo was placed in a duodenal loop.[1] One of the animals vomited after 30 minutes; the other showed no perceptible effects.

Three of the cats received intravenous injections of tartar emetic after vagotomy. A dose of 50 mg. per kilo in 20 parts of normal salt solution, injected in a period of about 15 seconds, caused death after 26 minutes during which time there were no signs of nausea. Each of the other two cats received doses of 35 mg. per kilo in 30 parts of normal salt solution. One of these showed slight, but unmistakable, signs of nausea after an interval of 3 minutes, and lasting about 50 minutes, after which a second dose similar to the first was administered. The cat died 15 minutes later without showing further signs of nausea. The second animal received two doses, each of 35 mg. per kilo, in the same way and died 2 minutes after the second dose without showing signs of nausea at any time.

The results of these experiments show that cutting the vagi in the cat inhibits the emetic action of large doses of tartar emetic, whether they be administered orally or intravenously, though such doses are capable of inducing nausea in some individuals after their administration in either way, and massive doses introduced into the stomach induce vomiting. Vagotomy appears to have much less influence on

[3] Cutting both vagi in the cat causes asphyxia unless the trachea is opened.

the action of tartar emetic on the duodenum, but though the total amounts used were much less than those required in the stomach, the amounts in the loops were far greater in proportion to the surface areas.

The effects of atropine on the action of tartar emetic are strikingly similar to those of vagotomy, but large doses are required to paralyze the vagus in the gastrointestinal tract. Though the intravenous injection of tartar emetic did not cause vomiting after the vagi had been cut, or large doses of atropine had been injected, it did induce nausea in some cases, and it is fair to presume that vomiting might be induced in a small percentage of numerous experiments.

3. Experiments on the Eviscerated Animal.

We have investigated this phase of the problem by means of experiments on animals that had been eviscerated in the manner described by Eggleston and Hatcher for the study of the emetic action of apomorphine. Two experiments were performed on cats; both of the animals vomited within a few minutes after the intravenous injection of tartar emetic, showing that the poison is capable of inducing emesis in the cat in the absence of the entire gastrointestinal tract. These two experiments were essentially alike, except that one animal received a dose of 60 mg. of the poison per kilo, the other a dose of 40 mg. per kilo. The protocol of one of the experiments is given.

Protocol Showing the Emetic Action of Tartar Emetic in an Eviscerated Cat.— Cat, male; weight 2 kilos. Chloroform used for anesthesia. Mar. 23, 1922, 9.20 a.m. Completed operation for the removal of the gastrointestinal tract from the esophagus to the anus. Administration of chloroform stopped. 10.50 a.m. Animal walks about; condition good. 11.05 a.m. 40 mg. of tartar emetic per kilo, in 100 parts of normal salt solution, injected into femoral vein within a few seconds. 11.12 a.m. Vomited (typical vomiting movements with the expulsion of mucus from the esophagus). Animal killed.

4. The Action of Tartar Emetic on the Heart.

Hatcher and Weiss found that when cats are poisoned with digitalis bodies afferent impulses pass up from the heart to the vomiting center mainly by way of the vagus in some, mainly by way of the sympathetic nerve in others, such differences being due to differences in the

paths with different digitalis bodies, and also to differences in the paths with a single drug in different individuals. They found that simultaneous vagotomy and extirpation of the stellate ganglia prevent vomiting and all signs of nausea following the administration of any of the digitalis bodies which they studied. Since vagotomy does not invariably prevent nausea following the intravenous injection of tartar emetic, and since the poison is known to exert a toxic action on the heart, it seemed probable that the heart is the seat of the vomiting reflex.

Two cats were used for these experiments. A tracheal cannula was inserted, the vagi were cut, and the stellate ganglia were extirpated.[1] After an interval of about 2 hours in each experiment tartar emetic, dissolved in 20 parts of normal salt solution, was injected intravenously at once. Neither animal showed the least trace of nausea. The first animal received a dose of 60 mg. per kilo and died after an interval of 25 minutes. The second received a dose of 30 mg. per kilo and since it did not show the least sign of nausea during the succeeding 63 minutes, it was then given a dose of mercuric chloride through a stomach tube in order to determine whether the cat was still capable of vomiting. Emesis occurred atypically after 14 minutes and the animal was then killed.

The results of these experiments point to the heart as a seat—not necessarily the only one—of the emetic action of intravenous doses of tartar emetic. The protocol of the second of these experiments is given.

Protocol Showing that the Intravenous Injection of Tartar Emetic Is Incapable of Causing Nausea or Vomiting in the Cat after the Vagi Have Been Cut and the Stellate Ganglia Extirpated.—Cat, male; weight 2.6 kilos. Chloroform used for anesthesia. May 11, 1922, 10.00 to 10.30 a.m. Tracheal cannula inserted; the vagi cut; the stellate ganglia extirpated. 12 m. Animal coughed up mucus that had accumulated in esophagus; no sign of nausea. 1.15 p.m. 25 cc. of feebly acidulated water injected through stomach tube. 1.19 p.m. 30 mg. of tartar emetic per kilo, in 20 parts of normal salt solution, injected into femoral vein. 1.20 p.m. Lies on side; regurgitated a little water; no gastric contents expelled. 1.25 p.m. Much depressed. 2.05 p.m. Condition much improved, walks about. 2.10 p.m. Sits up in cage. 2.20 p.m. Licks fur (cleaning itself). No sign of nausea at any time. 2.22 p.m. 100 mg. of mercuric chloride per kilo 1:100 through stomach tube. 2.36 p.m. Vomited; unable to get up; no retching preceded vomiting. 2.40 p.m. Killed.

The results of this experiment show that the animal was capable of vomiting, though the tartar emetic failed to induce nausea. The

regurgitated fluid apparently consisted of the acidulated water that probably remained in the esophagus because of closure of the cardia due to the cutting of the vagi. The occurrence of regurgitation within a minute after the intravenous injection of the tartar emetic shows that it was not caused by the poison.

5. *The Rôle of the Abdominal Organs.*

It is conceivable that the irritation of almost any tissue in the body may give rise to the vomiting reflex, and, on the other hand, it might be supposed that the operative procedure involved in cutting the vagi and extirpating the stellate ganglia might have interfered with the emetic action of tartar emetic in the two experiments described, though, as already shown, mercuric chloride caused emesis. It is not feasible to investigate every possible seat of this emetic action, but we conducted two experiments designed to serve as controls of the preceding, so far as the question of interference by the operative procedure is concerned, and to determine whether the abdominal organs, other than the stomach and intestines, are concerned in the emetic action of tartar emetic.

The celiac ganglion, with the adjacent nerve tissue, was removed[1] in each of two cats which subsequently received an intravenous injection of tartar emetic. The first one showed great depression and was obviously poorly suited for the experiment, nevertheless, after an interval of about 1½ hours a dose of 60 mg. of tartar emetic per kilo, in 20 parts of normal salt solution, was injected intravenously. Defecation, the significance of which is closely related to that of vomiting, occurred after an interval of 36 minutes, and the animal died about 12 minutes later without showing signs of nausea.

The vagi were cut just below the level of the diaphragm in addition to the extirpation of the celiac ganglion in the second experiment.[1] After an interval of about 2½ hours a dose of 30 mg. of tartar emetic per kilo, in 30 parts of normal salt solution, was injected intravenously. Nausea was induced after 3 minutes, and vomiting occurred 4 minutes after the injection of the poison. The positive result in this experiment rendered further experiments of this type unnecessary.

We had no reason to doubt the correctness of Thumas' statement that the application of tartar emetic to the vomiting center caused depression so that emesis could not then be induced, but we did repeat his experiment in part, using one dog and two cats.[1] The tissues embraced in the vomiting center (about 10 sq. mm. in the dog) prob-

ably constitute not more than 1 in 75,000 parts of the total weight of the animal, hence only very small amounts of effective drugs are needed by direct application to this area to induce emesis.

The application of 0.0005 mg. of tartar emetic per kilo of weight in 5,000 parts of normal salt solution, in the first experiment on a dog, was followed by the application of three times that amount in a solution of five times the concentration. These doses were ineffective and the application of apomorphine then produced vomiting within 2 minutes.

The application of 0.0017 mg. of tartar emetic per kilo of weight, in 5,000 parts of normal salt solution, was ineffective in one cat, and the application of 0.35 mg. per kilo, in 20 parts of normal salt solution, was ineffective in another. About 5 mg. of tartar emetic (total) were then dusted onto the vomiting center of the second cat. There was little perceptible effect except moderate depression. The administration of 50 mg. of mercuric chloride per kilo, in 100 parts of water, through a stomach tube caused emesis after 27 minutes, after which the animal was killed.

We did not investigate the question of the effect of tartar emetic on the vomiting center further, but it is noteworthy that the direct application of such a relatively massive dose of powdered tartar emetic (not to mention the very large first dose used in the third experiment) to the vomiting center in the cat failed to induce depression such as Thumas observed in the dog.

DISCUSSION.

We have already mentioned certain salient points in the literature relating to the mechanism of vomiting induced by tartar emetic, and the results of our experiments may be discussed briefly.

Physiologists had only vague ideas concerning the mechanism of emesis previous to the publication of the paper by Thumas, and the greater number of those who studied the action of tartar emetic sought to explain it with reference to the gastrointestinal tract or to the central nervous system. We have already cited an example of this tendency, which still exists, in the argument that the presence of traces of antimony in the first vomitus following the intravenous injection of the poison indicates that emesis is induced reflexly from the gastrointestinal tract in such cases.

It is remarkable that the failure of Thumas to induce emesis by placing tartar emetic directly on the vomiting center did not lead to the investigation of the problem along new lines, and it is especially remarkable in view of the reiterated statement of Harnack with reference to the muscular action of emetics, and the well known fact that tartar emetic poisons the heart severely. Apparently the prestige of Hermann's name gained acceptance for the work of his pupils without

critical analysis, and the conclusions of Nobiling, Grimm, and Kleimann and Simonowitsch served mainly to introduce confusion into this difficult problem.

The coincidence of cardiac and emetic actions in numerous drugs directed our attention to the heart as the probable seat of the emetic action of tartar emetic, but we felt constrained to analyze the basis of accepted views and to attempt to explain why different investigators came to such discordant conclusions.

We have called attention elsewhere (Hatcher and Weiss) to the fact that vomiting, or the third stage at least, is of the nature of a convulsion, strictly comparable to the convulsions induced by strychnine, and that it results from abnormally severe sensory impulses acting on a normal vomiting center, or from normal sensory impulses acting on an abnormally sensitive vomiting center, such as that observed after the local application of apomorphine, strychnine (Magnini and Bartolomei), or brucine[4] to the vomiting center.

It is well known that nausea is induced by mild stimuli, similar to, but weaker than, those that cause vomiting in the normal animal, and we have found that such mild stimuli cause emesis when the vomiting center is rendered abnormally sensitive by the application of apomorphine. It seems probable, therefore, that the sensory impulses induced in the heart by tartar emetic which pass up to the vomiting center go mainly by way of the vagus, but that a few pass by way of the sympathetic nerve and the stellate ganglia, and that when the vagi are cut the intravenous injection of tartar emetic sometimes causes nausea by means of the few impulses which then pass up through the sympathetic nerve, but that these do not suffice to set up the convulsive movements of the third stage of vomiting. When the vagi are cut and the stellate ganglia are extirpated no impulses can pass from the heart to the vomiting center, and the intravenous injection of even a fatal dose of tartar emetic does not induce nausea.

Atropine has much the same effect as cutting the vagi on the emetic action of tartar emetic, however it is administered; this involves the action of atropine on the afferent nerve ends of the vagus. When the vagi are cut, or sufficient amounts of atropine are administered, the oral administration of a large dose of tartar emetic sometimes causes

[4] Unpublished observations in this laboratory.

nausea, but it seldom causes emesis. We cannot say that it never does, and, in fact, it seems probable that if a large amount of tartar emetic should pass the pylorus rapidly, emesis would result, for neither vagotomy nor the largest doses of atropine are capable of preventing vomiting following the introduction of large doses of tartar emetic into a small loop of the duodenum immediately below the pylorus, and massive doses of tartar emetic irritate the gastric mucosa sufficiently to induce vomiting after the vagi have been cut, or after a massive dose of atropine has been injected.[5]

All of the facts that we have presented seem to show that the afferent emetic impulses induced in the gastrointestinal tract by tartar emetic pass equally well by way of the vagus or the sympathetic nerve, and that the path depends on the innervation of the several parts of this tract rather than on any selective action of tartar emetic on the sensory endings[6] of the two types of nerves, the vagus being mainly concerned with the action on the gastric mucosa, probably the sympathetic nerve mainly with the action on the duodenal. The fact that atropine abolishes the afferent impulses in the one case and not in the other shows that there are two types of nerve endings concerned in the reflexes.

We are unable to offer any explanation of the fact that the afferent emetic impulses induced in the heart by tartar emetic pass upward mainly by way of the vagus, while those induced by certain of the digitalis bodies pass mainly by way of the sympathetic nerve, but this is certainly the case, and we were unable to induce vomiting by the intravenous injection of fatal doses of tartar emetic in animals in which the vagi had been cut, or in those which had received large doses of atropine. Nausea was induced in only one cat by the intravenous injection of tartar emetic after the intramuscular injection of atropine, and in only one by this means after the vagi had been cut.

Openchowski's contention that the vagus alone is concerned in the emetic action of tartar emetic must be modified, but it is probably true

[5] The problem of the quantitative antagonism between atropine and the emetic action of tartar emetic requires further study.

[6] It is not our purpose to offer any suggestion regarding the nature of the structures concerned with sensory impulses, and we use the word "endings" for the sake of convenience.

that it is chiefly concerned in many cases in which emesis is induced therapeutically, because nausea is induced readily in man by small doses of this poison; this results in closure of the pylorus, thus limiting the further action of the drug to the stomach for the greater part, and, as we have seen, the vagus is chiefly concerned with the emetic impulses from the stomach.

SUMMARY.

1. It has been shown that tartar emetic acts on the stomach to induce emesis after its oral administration, that only traces are present in the vomitus following its intravenous injection (Kleimann and Simonowitsch), and that it does not induce emesis when it is applied directly to the vomiting center (Thumas).

2. In the present study, which was made with cats except when otherwise specifically stated, the intravenous injection of tartar emetic caused emesis (typical vomiting movements) after the removal of the entire gastrointestinal tract from the esophagus to the anus.

3. Cutting the vagi inhibits emesis after the intravenous injection of any dose of tartar emetic, though nausea may be induced.

4. Cutting the vagi and simultaneously extirpating the stellate ganglia inhibits both nausea and vomiting after the intravenous injection of tartar emetic.

5. Extirpation of the celiac ganglion and simultaneous cutting of the vagi just below the level of the diaphragm does not prevent emesis following the intravenous injection of tartar emetic.

6. Cutting the vagi prevents vomiting after the introduction of large doses of tartar emetic into the stomach, but massive doses may still cause emesis. Vagotomy probably has less influence on the emetic action of a moderately large dose of tartar emetic introduced into a loop of the duodenum.

7. Atropine has very nearly the same effect on the emetic action of tartar emetic as cutting the vagi, but much larger doses are necessary to abolish the effect of the introduction of tartar emetic into the stomach in moderate amounts than that of equal amounts injected intravenously.

8. The facts just stated point to the heart as the seat of reflex vomiting following the intravenous injection of tartar emetic.

9. The intravenous injection of tartar emetic induces afferent emetic impulses which pass from the heart to the vomiting center mainly by way of the vagus, to a much less extent by way of the sympathetic nerve and the stellate ganglia.

10. The introduction of tartar emetic into the stomach induces afferent emetic impulses which pass upward mainly by way of the vagus, to a much less extent by way of the sympathetic nerve.

11. The introduction of tartar emetic into the duodenum induces afferent emetic impulses which pass upward partly by way of the sympathetic nerve, partly by way of the vagus.

12. It seems probable that the path taken by afferent emetic impulses induced in the gastrointestinal tract by tartar emetic depends on the innervation of the organ concerned, and not on any selective action of the poison on the afferent nerve.

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