NEUROINHIBITION IN THE REGULATION OF EMESIS*

J. ZABARA, R. B. CHAFFEE, JR., and M. F. TANSY

Dept. of Physiology and Biophysics, Temple University School of Dentistry, Philadelphia, Pa. 19140, U.S.A.

(Received 13 December, 1971)

Abstract. Elucidation of an inhibitory system in the regulation of emesis is presented in this report. Emesis preceded by retching, can be induced in the dog by appropriate electrical stimulation of abdominal vagus nerves at the supradiaphragmatic level. Failure to produce retching or emesis by electrical stimulation of the cervical vagus trunk suggests either that the abdominal vagal emetic afferent does not course in the cervical vagus or that fibers inhibitory to emesis are present. This report presents evidence for afferent fibers inhibitory to retching and emesis in the cervical vagus. Retching and emesis resulting from stimulation of the supradiaphragmatic vagus can be prevented by either transection of the cervical vagus or simultaneous stimulation of the cervical vagus trunk. In addition, retching and emesis occur with stimulation of a fine nerve bundle dissected from the cervical vagus trunk. That the afferent pathway inhibitory to retching and emesis involves pulmonary afferents is suggested by the observation that hyperventilation occurs with stimulation of the cervical vagus trunk.

1. Introduction

The contemporary model of the neural regulation of emesis is almost completely based upon excitatory systems involving the emetic center and chemoreceptor trigger zone (Borison and Wang, 1953; Wang, 1965). This report presents evidence that the excitatory system, which has been investigated intensively, acts in conjunction with an inhibitory system such that emesis is ordinarily prevented by a dominance of inhibition over excitation.

Although motion sickness studies involve most often emesis or retching as an 'end point', the excitatory system model of emetic regulation has been difficult to accomodate to mechanisms of motion sickness (Wood and Graybiel, 1968; Graybiel *et al.*, 1969). It may be that part of this difficulty has its origin in the previously unrecognized presence of an inhibitory system.

As is well known, emesis, preceded by retching, can be induced in the dog by appropriate electrical stimulation of the abdominal vagal afferent. Experimentally, stimulation is applied usually to the dorsal or ventral branches of the vagus at the supradiaphragmatic level. Retching and emesis, however, have not been observed with centripetal stimulation of the cervical vagus (Agostini *et al.*, 1957; DeBurgh and Evans, 1953; Evans and Murray, 1954; Rice and Joy, 1947; Schweitzer and Wright, 1936; Tansy *et al.*, 1968; Wyss, 1947). This repeated failure to elicit retching and emesis in the dog with central vagal stimulation at the cervical level suggests either the lack of an appropriate afferent in this region or the presence of an afferent pathway which is inhibitory to retching and emetic induction.

* Research supported by U.S.P.H.S. Grant No. FR05339-07.

Space Life Sciences **3** (1972) 282–292. *All Rights Reserved*
Copyright © 1972 by D. Reidel Publishing Company, Dordrecht-Holland

It has been demonstrated that gastric tension and mucosal chemoreceptor afferents of the abdominal vagus course in the cervical vagus (Iggo, 1956, 1957; Varbanova and Sokolov, 1967), but whether emetic afferents are included with these has never been established. For the most part, it has been taken for granted that the vagal emetic afferent courses the entire length of the nerve, but the possibility exists that vagal afferents responsible for retching and emesis leave the vagus trunks before reaching the cervical level. This is suggested by the work of Harper *et al.* (1935) who traced two groups of visceral afferent fibers in the feline vagus, one which follows both trunks to the medulla and the other which leaves the trunks in the thorax to follow intercostal nerves to the spinal cord. Of greater relevance may be the more recent findings of Geisel and associates (1965) who in the dog also found an extravagal system that reaches the stomach by way of the spinal cord. If, on the other hand, we assume that the abdominal vagal emetic is present in the cervical vagus, then an explanation is required as to why combined stimulation of the vagal emetic and non-emetic afferents at this level prevents the onset of emesis.

The purpose of the present study was to investigate the ultimate course of the abdominal vagal emetic afferents, and to determine if emetic inhibition can be evoked with cervical vagal stimulation.

2. Methods

Twenty-four fasted, and four non-fasted mongrel dogs of both sexes weighing between 9 and 25 kg, anesthetized with intravenous alpha glucochloralose (Chloralose) (100 mg/kg), were used in acute experiments. Supplemental anesthesia as dictated by the needs of the animal was given through an indwelling catheter in the right femoral vein. Through a midline incision low in the neck, a tracheostomy was established in all animals for either recording intratracheal pressure with a PT5A Grass transducer or maintaining artifical respiration. Right femoral arterial pressure was recorded continuously using a P23AC Statham transducer. Retching movements were recorded by a pressure cuff* wrapped around the animal's abdomen and connected to a PT5A Grass transducer. All three variables were charted on a Grass Model 7 polygraph.

Both vago-sympathetic trunks were exposed high in the neck while through an incision in the left seventh intercostal space, dorsal and ventral branches of the esophageal vagus were dissected and isolated from the level of the diaphragm to the level of the hilus of the lung. In four of the animals, the vago-sympathetic was freed from its sympathetic component by locating the superior cervical ganglion and dividing the common sheath holding together the preganglionic nerve and the vagus. In six others, a full lateral thoracotomy was performed thereby exposing the vagus in almost its entirety. Care was given in all these preparations to eliminate excessive connective tissue and to avoid drying of the nerve tissue.

The identity of the vagal afferents causing retching and emesis was determined by a process of separation of fine nerve bundles from the cervical vagus, accomplished by gentle teasing with specially prepared glass rods (Iggo, 1956). If retching or emesis

* Baumanometer, W. A. Baum Co., New York.

was not apparent upon stimulation of such a bundle, the process was repeated until the desired response was obtained.

Stimulation was carried out with a bipolar platinum electrode with the terminals spaced approximately 3–4 mm apart connected to a Model S8 Grass stimulator. The stimulator could deliver comparable square wave pulses simultaneously through two separate outputs via isolation transformers. The stimulus pattern was monitored at the nerve site with a Tektronix 564 oscilloscope.

3. Results

The purpose of the initial series of experiments was to compare the effect of stimulation of the vagus nerves at the diaphragmatic level with that at the cervical level on the induction of emesis. The stimulus parameters employed ranged from 1 to 125 Hz, 1 to 5 msec duration, and 1 to 15 V peak amplitude.

Stimulation of the transected or intact supradiaphragmatic vagus readily caused emesis, preceded by retching at a threshold frequency of about 4 to 8 Hz but the response was rarely obtained with frequencies above 60 Hz (Figure 1). Although the latent period for retching varied from 10 to 70 s, the stimulus parameters had no direct relationship to the duration of the latency. The stimulus was terminated at the initiation of retching which then continues for a total duration of 20 to 40 s. The abdominal movements in retching have a decreasing frequency beginning at approximately 1.5 Hz.

Hyperventilation occurs during stimulation of the right or left cervical vagus trunk at a threshold frequency of 2 to 6 Hz followed by a series of frequencies initiating a maximal duration of hyperventilation which decreases at increasing frequencies of stimulation (Figure 2). An apneic period occurs before or during the hyperventilation response at about 70 to 125 Hz. There is a latency of 2 to 5 s in onset of hyperventilation. The magnitude of the response is not constant for repeated trials of the same stimulus. Stimulation of the cervical vagus after separation of the preganglionic nerves to the superior cervical ganglion did not alter the response.

The following experiment was to determine what effect impulses in the cervical vagus might have on retching or emesis. Stimulation of either cervical vagus simultaneously with the abdominal vagus nerves prevents the initiation of retching and emesis (Figure 2). Once retching has been initiated, however, cervical vagal stimulation has no effect. Terminating or decreasing the stimulus voltage of the cervical vagus, leaving the supradiaphragmatic vagal stimulus, allows the occurrence of retching and emesis (Figure 3).

The following experiment was to determine the site along the vagus nerve, exposed from the diaphragm through the cervical region, at which retching and emesis appear. Stimulation along the vagus nerve between the cervical and diaphragmatic levels revealed that in more than 95% of all observations, retching and emesis could not be initiated cephalad to the entrance of the pulmonary branches of the vagus, but could be produced caudal to the pulmonary branches.

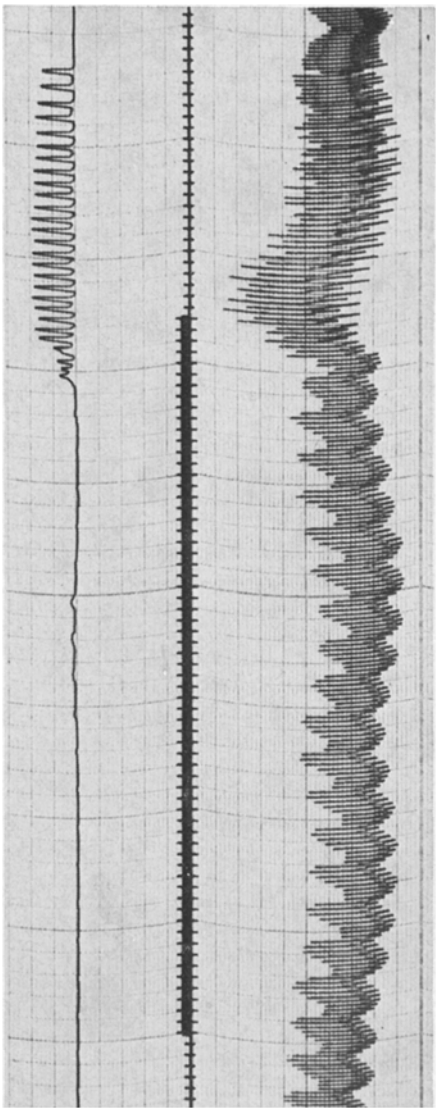

Fig. 1. Retching due to supradiaphragmatic vagal stimulation. Vertical marks on stimulus monitor record in this and other figures show 1 s. *Note latency corresponding to the initiation of abdominal movements in retching.*

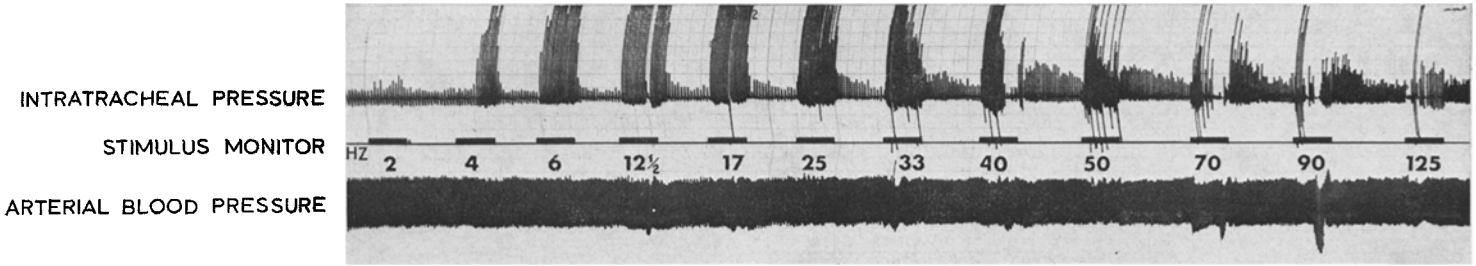

Fig. 2. Hyperventilation due to cervical vagus stimulation with increasing frequencies. Frequencies of stimulation (Hz) are stated below each stimulus monitor record. Voltage and pulse duration are constant at 4 V and 1 msec pulse duration. Note occurrence of apneic period with increasing frequencies of stimulation. Time is measured by each vertical grid division at 10 s.

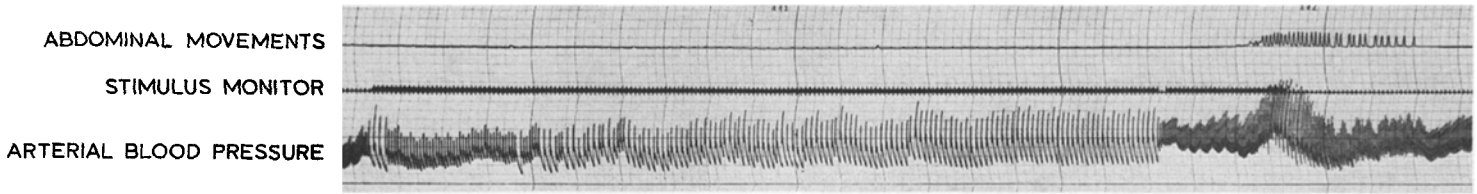

Fig. 3. The effect of simultaneous cervical and supradiaphragmatic vagal nerve stimulation. The cervical vagal stimulus is decreased at the gap in the stimulus monitor record leaving the original supradiaphragmatic vagal stimulation. Note the absence of retching until the decrease of the cervical vagal stimulus.

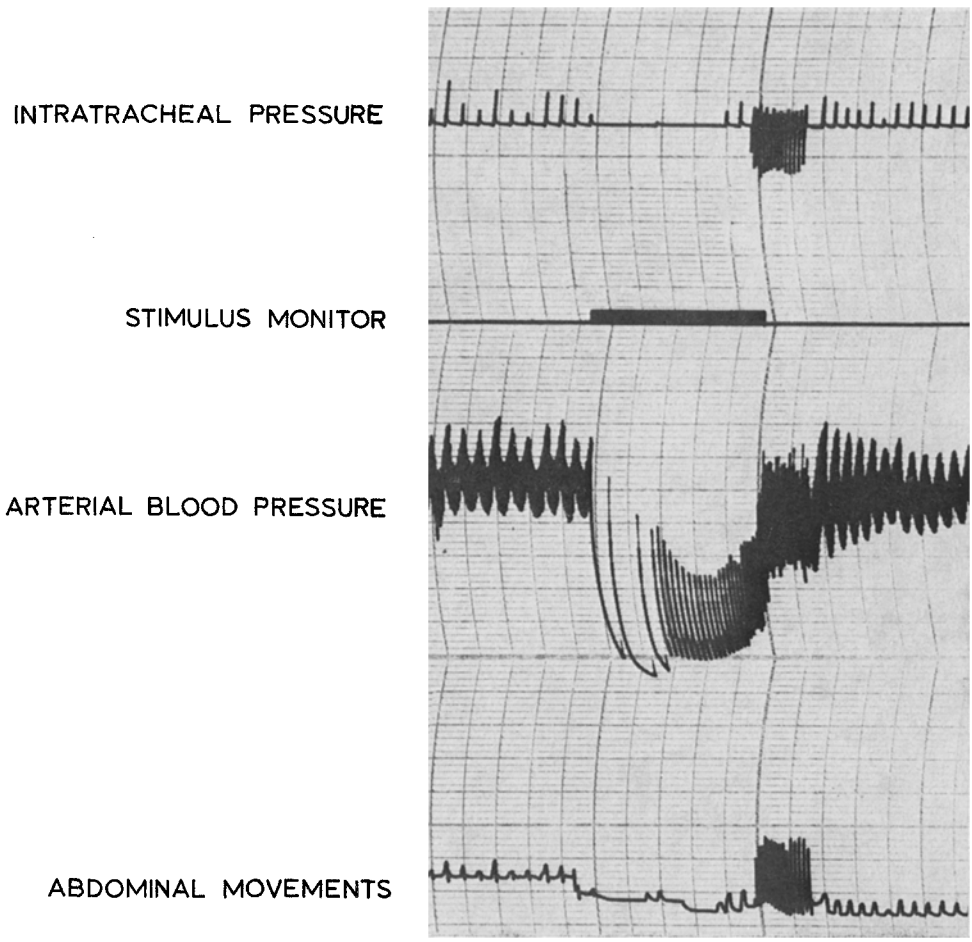

Fig. 4. Retching preceded by apnea, due to stimulation of a nerve bundle dissected from the cervical vagus. Note close correspondence between intratracheal pressure fluctuations and abdominal movements. Time is measured by each vertical grid division at 10 s.

Fine nerve bundles dissected from the cervical vagus trunk were stimulated with the same parameters as in the first series of experiments. Apnea occurs less than a second after the onset of stimulation of almost all nerve strands. Emesis, preceded by retching, occurs following apnea with the stimulation of a subgroup of these nerve bundles. This response is in all observable characteristics identical to that caused by supradiaphragmatic vagal stimulation (Figure 4). Abdominal movements and intratracheal pressure fluctuations in retching occur with the same frequency.

Arterial blood pressure responses to cervical vagal stimulation were variable in the above experiments depending upon whether the cervical vagi were intact or transected. The circulatory responses to stimulation of the supradiaphragmatic vagus were simular to that reported by Chapman *et al.* (1954) in unanesthetized dogs.

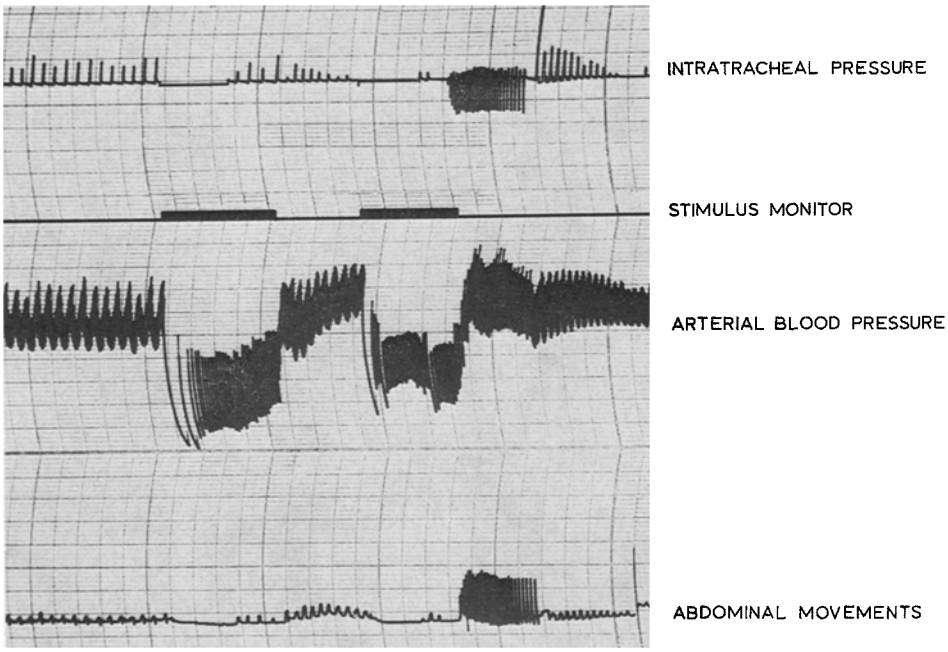

Fig. 5. Effects of stimulation of a nerve bundle causing retching or emesis with an apneic nerve bundle. The first stimulation is of the apneic nerve bundle alone; the second stimulation is simultaneously that of both nerve bundles. Time is measured by each vertical grid division at 10 s.

An investigation was also undertaken to determine if retching and emesis induced by stimulation of a fine nerve bundle could be prevented by simultaneous stimulation of the accompanying ipsilateral nerve bundles or the contralateral vagus. It is interesting to note that in three instances retching and emesis did not occur during the supposed stimulation of the vagal emetic and non-emetic afferent. However, this result could not be readily reproduced, for in all other instances retching and emesis occurred during simultaneous stimulation (Figure 5).

4. Discussion

Why centripetal stimulation of the cervical vagus trunk does not readily initiate retching or emesis has been investigated in these experiments. The inability of abdominal vagal afferent stimulation to initiate emesis after the cervical vagi have been transected indicates that the emetic afferents indeed do travel in the cervical vagus. This is supported by the separation from the vagus of a fine nerve bundle which upon stimulation initiates retching or emesis, whereas not only does stimulation of the intact trunk rarely produce retching or emesis but prevents their onset. These results can be reconciled by the consideration that certain vagal afferents in the cervical vagus, other than the abdominal afferents (Agostini *et al.*, 1957; Evans and Murray, 1954) can pre-

vent the initiation of retching or emesis. That the vagal afferents preventing retching or emesis are pulmonary afferents is suggested by the hyperventilatory response to trunk stimulation and the usual absence of retching or emesis by stimulation cephalad to the entrance of the pulmonary branches of the vagus.

However, an apparent contradiction to this suggestion is that retching or emesis produced by stimulation of a fine nerve bundle from the cervical vagus could be prevented only infrequently with simultaneous stimulation of the remaining fibers or contralateral vagus. But apnea, and not hyperventilation, always began with stimulation of the fine nerve bundle and therefore prior to retching. Perhaps the basis of this response is similar to spinal cord integrative processes such as reciprocal inhibition which relate to the action of antagonist muscles. Thus, it can be considered that apnea is compatible with retching or emesis and therefore impulses in these vagal afferents would not be expected to prevent emesis. Since ventilation of the lungs momentarily ceases during emesis (Hatcher, 1924), the hyperventilatory response can be considered as antagonistic to emesis and therefore impulses in these vagal afferents might be expected to inhibit retching and emesis.

It is suggested that the prevention of retching or emesis is due to central inhibition by the appropriate vagal afferents. It has been demonstrated that stimulation of the cervical vagus can cause inhibition of laryngeal reflexes due to vagal afferents which apparently produce a primary afferent depolarization, indicating presynaptic inhibition, in the region of the nucleus of the solitary tract (Rudomin, 1967). The afferent vagal fibers producing this inhibition appear to arise from the pulmonary stretch receptors (Rudomin, 1967). These observations are consistent with the possibility of inhibition in our experiments. Further, it has been indicated that presynaptic inhibition can be maintained for long periods of time (Dempsher *et al.*, 1959; Dempsher and Zabara, 1960).

Hwang *et al.* (1947) suggested twenty-five years ago the possibility of inhibition of emesis by vagal fibers in their statement: "On the basis of the small amount of data available we do not like to venture the suggestion that some normal inhibitory effect on the vomiting center is removed after vagotomy but this possibility should be borne in mind". Their data demonstrated that emesis was a common consequence after vagotomy was done at, and especially higher than, the level of the hilus of the lung. In addition, they found that the vomiting center was more susceptible to the action of apomorphine after vagotomy but Borison and Wang (1953) do not agree with this finding. Although they reserved judgement as to an inhibitory mechanism and concluded that there was the possibility of pharyngeal irritation being the basis of emesis, the present studies lend strong support to their initial suggestion of inhibition.

Borison and Wang (1953) clearly differentiate their definitions of retching and emesis. It is true that the present studies were designed to observe primarily retching and not emesis. This was done to prevent complications due to the efflux of vomitus from the animal's mouth. Also, it was possible to achieve a continuous recording of retching, whereas, by Borison's definition this was not possible for emesis. Further-

more, it was observed that supradiaphragmatic vagal stimulation and selected cervical fiber bundle stimulation produce emesis preceded by retching. It may be well to repeat the observation by Chapman *et al.* (1954) in this regard: "In addition, vomiting could be elicited and its presence was dependent upon a slight increase in the intensity or duration of the minimal current causing retching". These observations combined with the absence of retching or emesis with intact cervical vagal stimulation make it reasonable to suggest that inhibition of retching in these experiments is synonomous with inhibition of emesis. It must be emphasized that we have presented no observations or results of inhibition concerning emesis which is not preceded by retching. For the most part, emesis without retching has been reported only with medullary stimulation (Borison and Wang, 1953).

Although present experiments were performed with anesthetized animals, retching and emesis with supradiaphragmatic vagal stimulation has been demonstrated in conscious dogs with implanted electrodes by Chapman *et al.* (1954). There does not seem to be any important differences between the response in conscious dogs and those anesthetized with Chloralose. However, Chapman *et al.* (1954) did indicate that sodium pentobarbital has a depressive effect on retching and emesis.

It appears that the locus of the inhibition is not directly on the retching or emetic center since it was not possible to inhibit emesis after its initiation. The locus of inhibition could occur presumably in the nucleus of the tractus solitarius or at some possible intermediate synapse on the pathway to the retching or emetic center. This could be determined by appropriate placement or microelectrodes in these regions of the medulla.

The latency of emesis greatly exceeds even the longest conduction time of vagal abdominal afferents as measured by Iggo (1956). This long latency might be due to a summation of impulses in the emetic center which discharges when its critical threshold is reached. In this sense, emesis appears to be similar to an all-or-none response. Chapman *et al.* (1954) have stated an approximate latency of onset of emesis in the unanesthetized dog of twenty seconds. We have found the latency in the Chloralose anesthetized dog to be variable from about 10 s to 70 s. This is the longest latency known to the authors for a reflex arc. Thus, an important question is the locus of the major portion of this latency. There are three main elements involved in the latency: conduction time in the afferent and efferent nerves; neuromuscular delay and muscular contraction time, and central nervous system. The first two elements should involve less than a second in latency based upon commonly accepted measurement (Bard, 1961). Thus, it appears that the latency primarily occurs in the brain or spinal cord. It seems reasonable that the primary central site for the latency is the emetic center in the medulla although direct electrical recording is necessary to establish this.

Consideration must be given to the possibility that the central cervical vagal stimulus produces a polarization block of the retching or emetic afferent impulses initiated at the diaphragmatic level. This is not likely because: (1) stimulation of the right or left cervical vagus separately can prevent retching or emesis, thus leaving

unaffected the emetic afferents coursing in the non-stimulated vagus trunk, and (2) stimulation of the fine nerve bundle dissected from one cervical vagus trunk can initiate retching or emesis, thus demonstrating that unilateral afferents can initiate bilateral efferent impulses producing retching or emesis.

Previous research (Rice and Joy, 1947; Wyss, 1947) has not demonstrated a hyperventilatory response as great as that observed in these experiments. This might be due to the anesthetic utilized in the present experiments. However, Rice and Joy (1947) did observe with an increase in frequency of stimulation, a change from increased respiration to that of apnea in the dog. Also, Borison (1948) observed a marked 'spasmodic respiration' from electrical stimulation of the medulla.

It is not certain whether there are specific afferents in the vagus which only initiate retching and emesis or whether, as is more likely, a number of afferents, such as from the tension receptors and chemoreceptors of the stomach and intestine (Iggo, 1956, 1957) also are capable of producing retching and emesis under the appropriate conditions.

Although the reflex coordination of emesis and respiration is a complex problem, it is apparent that inhibition is a primary component of this coordination. The emetic response is based upon a balance between the central excitatory and inhibitory states in the emetic center. The inhibitory state receives a strong contribution from vagal pulmonary afferents which can constitute the basis for absence of emesis with centripetal stimulation of the cervical vagus.

Thus the effect of excitatory impulses delivered to the emetic center, whether in motion sickness or otherwise, can be prevented by pulmonary afferent inhibition. It is reasonable to suppose that this is not the only system exerting inhibition upon the emetic center. For instance, emetic inhibition might also emanate from the sensory cortex. However, a possible conclusion is that appropriate patterns of respiration might, at least temporarily, prevent the onset of emesis. Further investigation in this area might thus lead to a physiological method for the alleviation of nausea and emesis in motion sickness. It is interesting to note that Lipana *et al.* (1969) actually increased nausea and vomiting in angular acceleration studies by utilizing various respiratory maneuvers which generally would tend to decrease or stop appropriate pulmonary afferent impulses.

Further, the vomiting center and reticular formation are juxtaposed in the brain stem, so that state of consciousness and emesis might be correlated in motion sickness. In fact, it was demonstrated that drowsiness also occurs in Coriolis accelerations and continues long after the nausea syndrome has disappeared (Graybiel *et al.*, 1969). Thus an inhibitory system for emesis might correspond to a similar inhibition of the reticular formation resulting in a lowered state of consciousness. Also, inhibition may play a significant role in the variable intensities of motion sickness produced even in select populations with similar vestibular response characteristics (Miller *et al.*, 1969). Thus, neuroinhibition in emetic regulation might constitute an important basis for investigation of motion sickness which continues to be a serious problem for flying personnel (Dowd *et al.*, 1971; Ryback *et al.*, 1970).

References

Agostini, E., Chinnock, J. E., DeBurgh, D. M., and Murray, J. G.: 1957, *J. Physiol.* **135**, 182–205.
Bard, Phillip (ed.): 1961, *Medical Physiology*, 11th ed., St. Louis C. V. Mosby Co.
Borison, H. L.: 1948, *Am. J. Physiol.* **154**, 55–62.
Borison, H. L. and Wang, S. C.: 1953, *Pharmacol. Rev.* **5**, 193–230.
Chapman, W. P., Wilkins, E. W., and Von Heuber, E.: 1954, *Surgery, Obstetr. Gynecol.* **98**, 579–595.
DeBurgh, D. M. and Evans, D. H. L.: 1953, *J. Physiol.* **120**, 579–595.
Dempsher, J., Tokumaru, T., and Zabara, J.: 1959, *J. Physiol.* **146**, 428–437.
Dempsher, J. and Zabara, J.: 1960, *J. Physiol.* **151**, 217–224.
Dowd, P. J., Cramer, R. L., and Hanna, H. H.: 1971, *Aerospace Med.* **42**(7), 703–705.
Evans, D. H. L. and Murray, J. G.: 1954, *J. Anat.* **88**, 320–333.
Graybiel, A.: 1964, *Aerospace Med.* **40**(4), 351–367.
Graybiel, A., Deane, F. R., and Colehour, J. K.: 1969, *Aerospace Med.* **40** (2), 142–148.
Geisel, A., Aria, T., Jefferson, N., and Necheles, H.: 1965, *Am. J. Gastroent.* **44**, 551–558.
Harper, A. A., McSwiney, B. A., and Suffolk, S. F.: 1935, *J. Physiol.* **85**, 267–276.
Hatcher, R. A.: 1924, *Physiol. Rev.* **4**, 479–504.
Hwang, K., Essex, H. E., and Mann, F. C.: 1947, *Am. J. Physiol.* **149**, 429–448.
Iggo, A.: 1956, *Quart. J. Exp. Physiol.* **42**, 130–143.
Iggo, A.: 1957, *J. Physiol.* **142**, 110–126.
Lipana, J. G., Fletcher, J., Brown, W., and Cohen, G.: 1969, *Aerospace Med.* **40**(9), 976–980.
Miller II, Earl F., Graybiel, A., Kellogg, R. S., and O'Donnell, R. D.: 1969, *Aerospace Med.* **40**(8), 862–868.
Rice, H. V. and Joy, M. S.: 1947, *Am. J. Physiol.* **149**, 24–42.
Rudomin, P.: 1967a, *J. Neurophysiol.* **30**, 964–981.
Rudomin, P.: 1967b, *Experientia* **23**, 117–119.
Ryback, R. S., Rudd, R. E., Matz, G. J., and Jennings, C. L.: 1970, *Aerospace Med.* **41**(6), 672–677.
Schweitzer, A. and Wright, S.: 1936, *J. Physiol.* **88**, 459–475.
Tansy, M. F., Mackowiak, R. C., and Friedman, M. H. F.: 1968, *Surgery, Gynecol. Obstetr.* **127**, 259–269.
Varbanova, A. and Sokolov, V.: 1967, *Acta Physiol. Acad. Scient. Hung.* **31**, 107–113.
VonBaumgarten, R. J., Baldrighi, G., Atema, J., and Shillinger, Jr., G. L.: 1971, *Space Life Sci.* **3**, 25–33.
Wang, S. C.: 1965, in *Physiological Pharmacology*, Vol. 2, Academic Press New York, pp. 255–328.
Wood, C. D. and Graybiel, A.: 1968, *Aerospace Med.* **39**(12), 1341–1344.
Wyss, O.: 1947, *J. Neurophysiol.* **10**, 315–320.